	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2003/06/17 14:01
2	L2	331546	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2003/06/17 14:02
3	L3	76345	promoter$1	USPAT; US-PGPUB	2003/06/17 14:02
4	L4	1383639	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2003/06/17 14:02
5	L5	60	2 near10 4 near10 3	USPAT; US-PGPUB	2003/06/17 14:03
6	L6	9302	pps or phosphoenol adj pyruvate adj synthase$1	USPAT; US-PGPUB	2003/06/17 14:29
7	L7	94	6 near4 (gene$1 or sequence$1)	USPAT; US-PGPUB	2003/06/17 14:29
8	L8	22	7 same (overexpress$ or amplif$10 or increas$8)	USPAT; US-PGPUB	2003/06/17 14:30
9	L9	17	7 and 2	USPAT; US-PGPUB	2003/06/17 14:48
10	L10	6285	lycopene$1 or isoprenoid$1 or carotene$1 or astaxanthin$1	USPAT; US-PGPUB	2003/06/17 14:58
11	L11	1	6 same 10	USPAT; US-PGPUB	2003/06/17 14:58
12	L12	1563	6 and 2	USPAT; US-PGPUB	2003/06/17 15:01
13	L13	1563	12 and 6	USPAT; US-PGPUB	2003/06/17 15:01
14	L14	3593	10 and 2	USPAT; US-PGPUB	2003/06/17 15:01
15	L15	9	14 and 6	USPAT; US-PGPUB	2003/06/17 15:01

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2003/06/17 14:01
2	L2	331546	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2003/06/17 14:02
3	L3	76345	promoter$1	USPAT; US-PGPUB	2003/06/17 14:02
4	L4	1383639	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2003/06/17 14:02
5	L5	60	2 near10 4 near10 3	USPAT; US-PGPUB	2003/06/17 14:03

PGPUB-DOCUMENT-NUMBER: 20030108986

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030108986 A1

TITLE: Compositions and methods comprising G-protein coupled receptors

PUBLICATION-DATE: June 12, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Communi, Didier	Dilbeek		BE	
Lannoy, Vincent	Brussels		BE	
Brezillon, Stephane	Brussels		BE	
Detheux, Michel	Mons		BE	
Parmentier, Marc	Brussels		BE	
Govaerts, Cedric	Brussels		BE	

APPL-NO: 10/ 079384

DATE FILED: February 20, 2002

RELATED-US-APPL-DATA:

child 10079384 A1 20020220

parent continuation-in-part-of 09885453 20010621 US PENDING

US-CL-CURRENT: 435/69.1, 435/320.1 , 435/325 , 435/7.1 , 530/350 , 536/23.5 , 800/8

ABSTRACT:

The present invention relates to G-protein coupled receptors and the nucleic acid molecules encoding them. The invention further relates to methods of screening for compounds which modulate the activity of one or more of the G-protein coupled receptors disclosed herein, and methods for modulating receptor activity. The invention also provides a natural ligand for one or more of the G-protein coupled receptors disclosed herein, and methods for identifying other natural ligands for these receptors.

RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. .sctn.120 to U.S. application Ser. No. 09/885,453, filed Jun. 20, 2001, which is incorporated herein by reference in its entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX (113):

[0238] Additional examples of transcriptional control elements that are responsive to changes in GPCR activity include, but are not limited to those responsive to the AP-1 transcription factor and those responsive to NF-.kappa.B activity. The consensus AP-1 binding site is the palindrome TGA(C/G)TCA (Lee et al., 1987, Nature 325: 368-372; Lee et al., 1987, Cell 49: 741-752). The AP-1 site is also responsible for mediating **induction by tumor promoters such as the phorbol ester 12-O-tetradecanoylphorbol-.beta.-acetate** (TPA), and are therefore sometimes also referred to as a TRE, for TPA-response element. AP-1 activates numerous genes that are involved in the early response of cells to growth stimuli. Examples of AP-I-responsive genes include, but are not limited to the genes for Fos and Jun (which proteins themselves make up AP-1 activity), Fos-related antigens (Fra) 1 and 2, I.kappa.B.alpha., ornithine decarboxylase, and annexins I and II.

PGPUB-DOCUMENT-NUMBER: 20030104478

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030104478 A1

TITLE: Natural ligand of G protein coupled receptor ChemR23 and uses thereof

PUBLICATION-DATE: June 5, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wittamer, Valerie	Waterloo		BE	
Communi, David	Braine le Chateau		BE	
Vandenbogaerde, Ann	Munchen		DE	
Detheux, Michel	Mons		BE	
Parmentier, Marc	Beersel		BE	

APPL-NO: 10/ 201187

DATE FILED: July 23, 2002

RELATED-US-APPL-DATA:

child 10201187 A1 20020723

parent continuation-of PCT/EP02/07647 20020709 US UNKNOWN

child 10201187 A1 20020723

parent continuation-in-part-of 09905253 20010713 US PENDING

non-provisional-of-provisional 60303858 20010709 US

US-CL-CURRENT: 435/7.1

ABSTRACT:

The present invention relates to a G-protein coupled receptor and a novel ligand therefor. The invention provides screeing assays for the identification of candidate compounds which modulate the activity of the G-protein coupled receptor, as well as assays useful for the diagnosis of a disease or disorder related to the dysregulation of G-protein coupled receptor signaling.

PRIORITY

[0001] This application claims priority under 35 U.S.C. .sctn.120 as a continuation in part of U.S. application Ser. No. 09/905,253, filed Jul. 13, 2001, which claims priority under 35 U.S.C. .sctn.119(e) to U.S. Provisional application No. 60/303,858, filed Jul. 9, 2001.

---------- KWIC ---------

Detail Description Paragraph - DETX (83):

[0178] Additional examples of transcriptional control elements that are responsive to changes in GPCR activity include, but are not limited to those responsive to the AP-1 transcription factor and those responsive to NF-.kappa.B activity. The consensus AP-1 binding site is the palindrome TGA(C/G)TCA (Lee et al., 1987, Nature 325: 368-372; Lee et al., 1987, Cell 49: 741-752). The AP-1 site is also responsible for mediating **induction by tumor promoters such as the phorbol ester 12-O-tetradecanoylphorbol-.beta.-acetate** (TPA), and are therefore sometimes also referred to as a TRE, for TPA-response element. AP-1 activates numerous genes that are involved in the early response of cells to growth stimuli. Examples of AP-1-responsive genes include, but are not limited to the genes for Fos and Jun (which proteins themselves make up AP-1 activity), Fos-related antigens (Fra) 1 and 2, I.kappa.B.alpha., ornithine decarboxylase, and annexins I and II.

PGPUB-DOCUMENT-NUMBER: 20030104356

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030104356 A1

TITLE: Compounds and methods for treating and screening viral reactivation

PUBLICATION-DATE: June 5, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Berger, Shelly L.	Wayne	PA	US	

APPL-NO: 10/ 108164

DATE FILED: March 26, 2002

RELATED-US-APPL-DATA:

child 10108164 A1 20020326

parent continuation-of 09424348 19991122 US ABANDONED

US-CL-CURRENT: 435/5, 424/186.1

ABSTRACT:

This invention relates to host cellular factors as therapeutic and diagnostic compounds, and methods using such factors for screening for antiviral compounds, particularly compounds useful to treat Herpesvirus infections, such as HSV-1 and HSV-2 infections.

---------- KWIC ---------

Detail Description Paragraph - DETX (309):
[0287] Varnum, B. C., Lim, R. W. & Herschman, H. R. (1989). Characterization of TIS7, a gene **induced in Swiss 3T3 cells by the tumor promoter tetradecanoyl phorbol acetate**. Oncogene 4, 1263-1265.

PGPUB-DOCUMENT-NUMBER: 20030096833

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030096833 A1

TITLE: Substituted ideno[1,2-c]isoquinoline derivatives and methods of use thereof

PUBLICATION-DATE: May 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Jagtap, Prakash G.	Beverly	MA	US	
Baloglu, Erkan	Boston	MA	US	
van Duzer, John H.	Georgetown	MA	US	
Szabo, Csaba	Gloucester	MA	US	
Salzman, Andrew L.	Belmont	MA	US	

APPL-NO: 09/ 944524

DATE FILED: August 31, 2001

US-CL-CURRENT: 514/285, 546/62 , 546/70

ABSTRACT:

The invention provides a novel class of substituted indeno[1,2-c]isoquinoline derivatives. Pharmaceutical compositions and methods of making and using the compounds, are also described.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (57):

[0053] The compositions may be sterilized and/or contain minor amounts of non-toxic adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution **promoters, salts for regulating the osmotic pressure pH buffering agents, and other substances such as for example, sodium acetate,** triethanolamine oleate, etc. In addition, they may also contain other therapeutically valuable substances.

PGPUB-DOCUMENT-NUMBER: 20030096299

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030096299 A1

TITLE: Natural ligand of G protein coupled receptor ChemR23 and uses thereof

PUBLICATION-DATE: May 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wittamer, Valerie	Waterloo		BE	
Communi, David	Braine le Chateau		BE	
Vandenbogaerde, Ann	Munchen		DE	
Detheux, Michel	Mons		BE	
Parmentier, Marc	Linkebeek		BE	

APPL-NO: 09/ 905253

DATE FILED: July 13, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60303858 20010709 US

US-CL-CURRENT: 435/7.1

ABSTRACT:

The invention relates to the identification of TIG2, the polypeptide product of Tazarotene-Induced Gene 2, as a natural ligand of the ChemR23 G protein coupled receptor (GPCR). The invention encompasses the use of the interaction of ChemR23 polypeptides and TIG2 polypeptides as the basis of screening assays for agents that modulate the activity of the ChemR23 receptor. The invention also encompasses diagnostic assays based upon the ChemR23/TIG2 interaction, as well as kits for performing diagnostic and screening assays.

[0001] This application claims priority to U.S. Provisional No: _____, filed Jul. 19, 2001.

---------- KWIC ---------

Detail Description Paragraph - DETX (82):

[0171] Additional examples of transcriptional control elements that are responsive to changes in GPCR activity include, but are not limited to those responsive to the AP-1 transcription factor and those responsive to NF-.kappa.B activity. The consensus AP-1 binding site is the palindrome TGA(C/G)TCA (Lee

et al., 1987, Nature 325: 368-372; Lee et al., 1987, Cell 49: 741-752). The AP-1 site is also responsible for mediating **induction by tumor promoters such as the phorbol ester 12-O-tetradecanoylphorbol-.beta.-acetate** (TPA), and are therefore sometimes also referred to as a TRE, for TPA-response element. AP-1 activates numerous genes that are involved in the early response of cells to growth stimuli. Examples of AP-1-responsive genes include, but are not limited to the genes for Fos and Jun (which proteins themselves make up AP-1 activity), Fos-related antigens (Fra) 1 and 2, I.kappa.B.alpha., omithine decarboxylase, and annexins I and II.

PGPUB-DOCUMENT-NUMBER: 20030078212

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030078212 A1

TITLE: PHARMACEUTICAL COMPOSITIONS CONTAINING POLY(ADP-RIBOSE) GLYCOHYDROLASE INHIBITORS AND METHODS OF USING THE SAME

PUBLICATION-DATE: April 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
LI, JIA-HE	COCKEYSVILLE	MD	US	
ZHANG, JIE	ELLICOTT CITY	MD	US	

APPL-NO: 09/ 182645

DATE FILED: October 30, 1998

CONTINUED PROSECUTION APPLICATION: This is a publication of a continued prosecution application (CPA) filed under 37 CFR 1.53(d).

US-CL-CURRENT: 514/22, 514/25

ABSTRACT:

The present invention relates to pharmaceutical compositions containing poly(ADP-ribose) glucohydrolase inhibitors, also known as PARG inhibitors, and methods of using the same for inhibiting or decreasing free radical induced cellular energy depletion, cell damage, or cell death. More particularly, the present invention relates to pharmaceutical compositions containing poly (ADP-ribose) glucohydrolase inhibitors such as glucose derivatives; lignin glycosides; hydrolysable tannins including gallotannins and ellagitannins; adenoside derivatives; acridine derivatives including 6,9-diamino-2-ethoxyacridine lactate monohydrate; tilorone analogs including tilorone R10.556, daunomycin or daunorubicin hydrochloride; ellipticine; proflavine; and other PARG inhibitors; and their method of use in treating or preventing diseases or conditions due to free radical induced cellular energy depletion and/or tissue damage resulting from cell damage or death due to necrosis, apoptosis, or combinations thereof.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (29):

[0028] The use of the PARG inhibitor tannic acid for treating HIV infection is discussed in Uchiumi et al., "Inhibitory Effect of Tannic Acid on Human Immunodeficiency Virus **Promoter Activity Induced by 12-O-Tetra Decanoylphorbol-13-acetate** in Jurkat T-Cells", Biochem. Biophys. Res. Comm.

220:411-417 (1996).

PGPUB-DOCUMENT-NUMBER: 20030050235

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030050235 A1

TITLE: Natural ligand for orphan G protein coupled receptor GPR86 and methods of use

PUBLICATION-DATE: March 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Communi, Didier	Dilbeek		BE	
Suarez, Nathalie	Bruxelles		BE	
Detheux, Michel	Mons		BE	
Brezillion, Stephane	Bruxelles		BE	
Lannoy, Vincent	Liernu		BE	
Parmentier, Marc	Linebeek		BE	
Boeynaems, Jean-Marie	Wemmel			BE

APPL-NO: 09/ 924125

DATE FILED: August 7, 2001

US-CL-CURRENT: 514/12, 435/7.21

ABSTRACT:

The present invention is related to a recombinant cell expressing a nucleotide sequence encoding a G protein coupled receptor having an amino acid sequence which presents more than 70% sequence identity with SEQ ID.NO.1 as well as to a drug screening method and kit using the orphan G protein coupled receptor GPR86, identified hereafter as receptor for ADP (P2Y.sub.13) and a homologous sequence, the corresponding polynucleotide and said recombinant cell to identify agonist, inverse agonist and antagonist compounds applicable to a diagnostic, prevention and/or treatment of various diseases and disorders.

---------- KWIC ---------

Detail Description Paragraph - DETX (112):

[0193] Additional examples of transcriptional control elements that are responsive to changes in GPCR activity include, but are not limited to those responsive to the AP-1 transcription factor and those responsive to NF-.kappa.B activity. The consensus AP-1 binding site is the palindrome TGA(C/G)TCA (Lee et al., 1987, Nature 325: 368-372; Lee et al., 1987, Cell 49: 741-752). The AP-1 site is also responsible for mediating **induction by tumor promoters such as the phorbol ester 12-O-tetradecanoylphorbol-.beta.-acetate** (TPA), and are therefore sometimes also referred to as a TRE, for TPA-response element. AP-1

activates numerous genes that are involved in the early response of cells to growth stimuli. Examples of AP-1-responsive genes include, but are not limited to the genes for Fos and Jun (which proteins themselves make up AP-1 activity), Fos-related antigens (Fra) 1 and 2, I.kappa.B.alpha., ornithine decarboxylase, and annexins I and II.

PGPUB-DOCUMENT-NUMBER: 20020192262

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020192262 A1

TITLE: 1'-Acetoxychavicol acetate for tuberculosis treatment

PUBLICATION-DATE: December 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Palittapongarnpim, Prasit	Bangkok		TH	
Kirdmanee, Chalermpol	Bangkok		TH	
Kittakoop, Prasat	Prathumthani		TH	
Rukseree, Kamolchanok	Bangkok		TH	

APPL-NO: 10/ 152570

DATE FILED: May 23, 2002

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
TH	066318	2001TH-066318	June 18, 2001

US-CL-CURRENT: 424/422

ABSTRACT:

1'-Acetoxychavicol acetate is a compound not known before to possess anti-tuberculous activity. The above data revealed that the compound was active against the standard H37Ra strain as well as several clinical isolates at the concentration well below the toxic concentration against various mammalian cells. The compound is therefore potentially useful as an therapeutic and preventive agent for tuberculosis as well as an antiseptic agent against the bacteria.

---------- KWIC ---------

Detail Description Paragraph - DETX (31):

[0046] 8. Kondo, A., Ohigashi, H., Murakami, A., Suratwadee, J., and Koshimizu, K. 1'-Acetoxychavicol **acetate as a potent inhibitor of tumor-promoter-induced** Epstein-Barr virus activation from Languas galanga, a traditional Thai condiment. Biosci Biotechnol Biochem 1993;57:1344-1345.

US-PAT-NO: 6506598

DOCUMENT-IDENTIFIER: US 6506598 B1
See image for Certificate of Correction

TITLE: Cell culture process

DATE-ISSUED: January 14, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Andersen; Dana C.	Redwood City	CA	N/A	N/A
Bridges; Tiffany M.	Burlingame	CA	N/A	N/A
Gawlitzek; Martin	Foster City	CA	N/A	N/A
Hoy; Cynthia A.	Hillsborough	CA	N/A	N/A

APPL-NO: 09/ 553924

DATE FILED: April 21, 2000

PARENT-CASE:

This is a non-provisional application claiming priority to provisional application no. 60/131,076 , filed Apr. 26, 1999, the entire disclosure of which is hereby incorporated by reference.

US-CL-CURRENT: 435/359, 435/252.3 , 435/358 , 435/69.6 , 530/395

ABSTRACT:

A glycoprotein is produced by a process comprising culturing mammalian host cells expressing nucleic acid encoding said glycoprotein in the presence of (a) a factor that modifies growth state in a cell culture, (b) a divalent metal cation that can adopt and prefers an octahedral coordination geometry, and/or (c) a plasma component. In this process, the occupancy of an N-linked glycosylation site occupied only in a fraction of a glycoprotein is enhanced. Such culturing is preferably carried out at a temperature of between about 30.degree. C. and 35.degree. C. and/or in the presence of up to about 2 mM of a butyrate salt and/or in the presence of a cell-cycle inhibitor.

23 Claims, 16 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 8

---------- KWIC ---------

Detailed Description Text - DETX (14):

By "plasma component" is meant a constituent of normal plasma. This would include growth **promoters and tumor-promoting agents for endothelial cell growth, regulators of differentiation of epithelial tissues, glucagon, heparin, phorbol myristate acetate,** PRL, thyroglobulin, 8Br-cAMP, thrombin, vitamin A and its derivatives (retinoids such as retinoic acid, e.g., beta-all-trans retinoic acid), glutathione, steroids such as corticosterone, cortisol, and corticoids, e.g., glucocorticoids such as hydrocortisone, and hormones, preferably those that are vital hormones of metabolism such as estrogen, insulin, and thyroid hormones, e.g., thyroxine and tri-iodothyronine (T.sub.3). The thyroid hormones are preferred, and most preferably thyroxine and tri-iodothyronine. Since some serum, including fetal calf serum, contains thyroid hormones and the thyroid hormone binding protein at nanomolar levels, it is preferred to use serum-free medium, particularly if thyroid hormones are employed to enhance site-occupancy.

US-PAT-NO: 6504048

DOCUMENT-IDENTIFIER: US 6504048 B1

TITLE: Flavorant compositions

DATE-ISSUED: January 7, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bachmann; Jean-Pierre	Wadenswil	N/A	N/A	CH
Gautschi; Markus	Zeiningen	N/A	N/A	CH
Hostettler; Bernhard	Gockhausen	N/A	N/A	CH
Yang; Xiaogen	West Chester	OH	N/A	N/A

APPL-NO: 09/ 634029

DATE FILED: August 8, 2000

PARENT-CASE:

This is a Continuation Application of U.S. application Ser. No. 09/212,985, now Pat. No. 6,203,839 filed Dec. 16, 1998, now Pat. No. 6,203,839 which is incorporated herein by reference in its entirety. This application is also related to application Ser. No. 09/634,067, filed on even date herewith and entitled "Flavorant Compositions", and is incorporated herein by reference in its entirety.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
EP	97122633	December 22, 1997

US-CL-CURRENT: 560/254, 426/533 , 426/538 , 426/546 , 560/221

ABSTRACT:

The invention is related to a flavorant composition containing 1'-acetoxychavicol acetate and 1'-acetoxyeugenol acetate derivatives thereof as well as a flavorant acceptable carrier. The flavorant composition may be used for flavoring foods, beverages or healthcare products with warm/hot, spicy and pungent sensations related to Galangal.

15 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Other Reference Publication - OREF (8):

Kondo, et al., 1'Acetoxychavicol **Acetate as a Potent Inhibitor of Tumor Promoter-induced** Epstein-Barr Virus Activation from Lanquas galanga, a Traditional Thai Condiment, Biosci. Biotech. Biochem. 57(8) (1993) 1344-1345.

US-PAT-NO: 6476252

DOCUMENT-IDENTIFIER: US 6476252 B1

TITLE: Flavorant compositions

DATE-ISSUED: November 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bachmann; Jean-Pierre	Wadenswil	N/A	N/A	CH
Gautschi; Markus	Zeiningen	N/A	N/A	CH
Hostettler; Bernhard	Gockhausen	N/A	N/A	CH
Yang; Xiaogen	West Chester	OH	N/A	N/A

APPL-NO: 09/ 634067

DATE FILED: August 8, 2000

PARENT-CASE:

This is a Continuation Application of U.S. application Ser. No. 09/212,985, filed Dec. 16, 1998, which is incorporated herein by reference in its entirety. This application is also related to application Ser. No. 09/634,029, filed on even date herewith and entitled "Flavorant Compositions", and is incorporated herein by reference in it entirety.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
EP	97122633	December 22, 1997

US-CL-CURRENT: 560/130

ABSTRACT:

The invention is related to a flavorant composition containing 1'-acetoxychavicol acetate and 1'-acetoxyeugenol acetate derivatives thereof as well as a flavorant acceptable carrier. The flavorant composition may be used for flavoring foods, beverages or healthcare products with warm/hot, spicy and pungent sensations related to Galangal.

1 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Other Reference Publication - OREF (7):

Kondo, et al., 1'Acetoxychavicol **Acetate as a Potent Inhibitor of Tumor Promoter-induced** Epstein-Barr Virus Activation from Languas galanga, a Traditional Thai Condiment, Biosci, Biotech. Biochem. 57(8) (1993) 1344-1345.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2003/06/17 14:01
2	L2	331546	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2003/06/17 14:02
3	L3	76345	promoter$1	USPAT; US-PGPUB	2003/06/17 14:02
4	L4	1383639	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2003/06/17 14:02
5	L5	60	2 near10 4 near10 3	USPAT; US-PGPUB	2003/06/17 14:03
6	L6	9302	pps or phosphoenol adj pyruvate adj synthase$1	USPAT; US-PGPUB	2003/06/17 14:29
7	L7	94	6 near4 (gene$1 or sequence$1)	USPAT; US-PGPUB	2003/06/17 14:29
8	L8	22	7 same (overexpress$ or amplif$10 or increas$8)	USPAT; US-PGPUB	2003/06/17 14:30

PGPUB-DOCUMENT-NUMBER: 20030059903

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030059903 A1

TITLE: Process for the production of L-amino acids using strains of the family enterobacteriaceae that contain an attenuated aceA gene

PUBLICATION-DATE: March 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Rieping, Mechthild	Bielefeld		DE	
Hermann, Thomas	Bielefeld		DE	

APPL-NO: 10/ 114048

DATE FILED: April 3, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60283384 20010413 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
DE	101 16 518.8	2001DE-101 16 518.8	April 3, 2001

US-CL-CURRENT: 435/106, 435/252.3

ABSTRACT:

A process for the production of L-amino acids, in particular L-threonine, in which the following steps are carried out:
(a) fermentation of the microorganisms of the family Enterobacteriaceae producing the desired L-amino acid, in which the aceA gene or nucleotide sequences coding therefor are attenuated, in particular are switched off,
(b) enrichment of the L-amino acid in the medium or in the cells of the bacteria, and
(c) isolation of the L-amino acid.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Application Serial No. 60/283,384, filed Apr. 13, 2001, the contents of which are incorporated herein by reference.

---------- KWIC ---------

Claims Text - CLTX (12):

11. The process of claim 1, wherein in the microorganism one or more of the genes selected from the following group is **overexpressed**: the thrABC operon coding for aspartate kinase, homoserine dehydrogenase, homoserine kinase and threonine synthase, the pyc **gene coding for pyruvate carboxylase, the pps gene coding for phosphoenol pyruvate synthase, the ppc gene** coding for phosphoenol pyruvate carboxylase, the pntA and pntB genes coding for transhydrogenase, the rhtB gene imparting homoserine resistance, the mqo gene coding for malate:quinone oxidoreductase, the rhtC gene imparting threonine resistance, and the thrE gene coding for threonine export.

PGPUB-DOCUMENT-NUMBER: 20030054503

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030054503 A1

TITLE: Process for the production of L-amino acids using strains of the family enterobacteriaceae that contain an attenuated dgsA gene

PUBLICATION-DATE: March 20, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Rieping, Mechthild	Bielefeld		DE	
Hermann, Thomas	Bielefeld		DE	

APPL-NO: 10/ 114043

DATE FILED: April 3, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60283384 20010413 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
DE	101 16 518.8	2001DE-101 16 518.8	April 3, 2001

US-CL-CURRENT: 435/106, 435/252.33

ABSTRACT:

A process for the production of L-amino acids, in particular L-threonine, in which the following steps are carried out:
(a) fermentation of the microorganisms of the family Enterobacteriaceae producing the desired L-amino acid, in which the dgsA gene or nucleotide sequences coding therefor are attenuated, in particular are switched off,
(b) enrichment of the L-amino acid in the medium or in the cells of the bacteria, and
(c) isolation of the L-amino acid.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Application Serial No. 60/283,384, filed Apr. 13, 2001, the contents of which are incorporated herein by reference.

---------- KWIC ---------

Claims Text - CLTX (12):

11. The process of claim 1, wherein in the microorganism one or more of the genes selected from the following group is **overexpressed**: the thrABC operon coding for aspartate kinase, homoserine dehydrogenase, homoserine kinase and threonine synthase, the pyc **gene coding for pyruvate carboxylase, the pps gene coding for phosphoenol pyruvate synthase, the ppc gene** coding for phosphoenol pyruvate carboxylase, the pntA and pntB genes coding for transhydrogenase, the rhtB gene imparting homoserine resistance, the mqo gene coding for malate:quinone oxidoreductase, the rhtC gene imparting threonine resistance, and the thrE gene coding for threonine export.

PGPUB-DOCUMENT-NUMBER: 20030049803

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030049803 A1

TITLE: Process for the production of L-amino acids using strains of the family enterobacteriaceae that contain an attenuated fruR gene

PUBLICATION-DATE: March 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Rieping, Mechthild	Bielefeld		DE	
Hermann, Thomas	Bielefeld		DE	

APPL-NO: 10/ 114073

DATE FILED: April 3, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60283384 20010413 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
DE	101 16 518.8	2001DE-101 16 518.8	April 3, 2001

US-CL-CURRENT: 435/106, 435/252.3

ABSTRACT:

A process for the production of L-amino acids, in particular L-threonine, in which the following steps are carried out:
(a) fermentation of the microorganisms of the family Enterobacteriaceae producing the desired L-amino acid, in which the fruR gene or nucleotide sequences coding therefor are attenuated, in particular are switched off, (
b) enrichment of the L-amino acid in the medium or in the cells of the bacteria, and
(c) isolation of the L-amino acid.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Application Serial No. 60/283,384, filed Apr. 13, 2001, the contents of which are incorporated herein by reference.

---------- KWIC ---------

Claims Text - CLTX (12):

11. The process of claim 1, wherein in the microorganism one or more of the genes selected from the following group is **overexpressed**: the thrABC operon coding for aspartate kinase, homoserine dehydrogenase, homoserine kinase and threonine synthase, the pyc **gene coding for pyruvate carboxylase, the pps gene coding for phosphoenol pyruvate synthase, the ppc gene** coding for phosphoenol pyruvate carboxylase, the pntA and pntB genescoding for transhydrogenase, the rhtB gene imparting homoserine resistance, the mqo gene coding for malate:quinone oxidoreductase, the rhtC gene imparting threonine resistance, and the thrE gene coding for threonine export.

PGPUB-DOCUMENT-NUMBER: 20030040103

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030040103 A1

TITLE: Fermentation process for the preparation of L-amino acids using strains of the family enterobacteriaceae

PUBLICATION-DATE: February 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Rieping, Mechthild	Bielefeld		DE	
Bastuck, Christine	Bielefeld		DE	
Hermann, Thomas	Bielefeld		DE	
Thierbach, Georg	Bielefeld		DE	

APPL-NO: 09/ 963668

DATE FILED: September 27, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60237610 20001004 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
DE	DE 100 48 605.3	2000DE-DE 100 48 605.3	September 30, 2000
DE	DE 100 55 516.0	2000DE-DE 100 55 516.0	November 9, 2000
DE	DE 101 30 192.8	2001DE-DE 101 30 192.8	June 22, 2001

US-CL-CURRENT: 435/252.3

ABSTRACT:

The invention relates to a fermentation process for the preparation of L-amino acids, especially L-threonine, in which the following steps are carried out:
a) fermentation of the microorganisms of the family Enterobacteriaceae producing the desired L-amino acid, in which microorganisms at least the pckA gene and/or the open reading frames yjfA and ytfP are, individually or jointly, attenuated and, in particular, switched off,
b) enrichment of the L-amino acid in the medium or in the bacterial cells, and
c) isolation of the L-amino acid.

---------- KWIC ---------

Claims Text - CLTX (7):

6. Process according to claim 1, wherein microorganisms of the family

Enterobacteriaceae in which one or more genes selected from the group comprising: 6.1 the thrABC operon coding for aspartate kinase, homoserine dehydrogenase, homoserine kinase and threonine synthase, 6.2 the pyc gene coding for pyruvate carboxylase, 6.3 the **pps gene** coding for phosphoenolpyruvate synthase, 6.4 the ppc gene coding for phosphoenolpyruvate carboxylase, 6.5 the pntA and pntB genes coding for transhydrogenase, 6.6 the rhtB gene for homoserine resistance, and 6.7 the rhtC gene for threonine resistance, 6.8 the gdhA gene coding for glutamate dehydrogenase are simultaneously **amplified** and, in particular, **overexpressed** are fermented for the preparation of L-amino acids.

PGPUB-DOCUMENT-NUMBER: 20030022218

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030022218 A1

TITLE: Gene targeting methods and vectors

PUBLICATION-DATE: January 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Burgess, Robert Marshall JR.	San Diego	CA	US	
Ji, Henry Hongjun	San Diego	CA	US	

APPL-NO: 10/ 185980

DATE FILED: June 26, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60300953 20010626 US

US-CL-CURRENT: 435/6, 435/320.1 , 800/13

ABSTRACT:

Methods and vectors are provided for the specific alteration of particular genetic loci in eukaryotic cells. One method includes the utilization of positive-positive selection (PPS) DNA vectors for the purpose of creating and identifying cells which have vector sequences integrated into the host cell genome via site-specific homologous recombination. The method also comprises the utilization of sequences encoding in vivo detectable markers for the identification of cells which have exogenous vector sequences integrated into the genome of the host cell, either via site-specific homologous recombination or nonhomologous recombination or insertion. The invention also includes vectors for creating modifications in eukaryotic cells.

RELATED APPLICATION DATA

[0001] The present application claims priority under 35 U.S.C. .sctn.119(e) to U.S. Provisional Application Serial No. 60/300,953 filed on Jun. 26, 2001, which is incorporated by reference herein.

---------- KWIC ---------

Detail Description Paragraph - DETX (38):

[0067] PPS vectors and methods as well as cotransformation methods are utilized for the purposes of creating and identifying cells which have

undergone site-specific homologous recombination between the vector and cellular endogenous genomic target sequences. The vectors substantially enrich for the identification of cells which have undergone said process. To "substantially enrich" refers to the ability to significantly **increase** the likelihood of identifying cells for which site-specific homologous recombination between the vector and cell DNA sequences. The significant **increase** in likelihood is at least two-fold of homologous recombination events when compared to nonspecific insertion or integration events, preferably at least 10-fold, more preferably at least 100-fold and even more preferably at least 10,000-fold. Substantially enriched cell populations derived from the use of PPS vectors include around 1%, more preferably 10%, and even more preferably 99% of cells isolated have undergone site-specific homologous recombination between **PPS vector sequences** and cellular endogenous genomic target sequences.

US-PAT-NO: 6573431

DOCUMENT-IDENTIFIER: US 6573431 B1

TITLE: Recombinant preduodenal lipases and polypeptides derivatives produced by plants, processes for obtaining them and their uses

DATE-ISSUED: June 3, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lenee; Philippe	Noumea	N/A	N/A	FR
Gruber; Veronique	Chamalieres	N/A	N/A	FR
Baudino; Sylvie	Orcines	N/A	N/A	FR
Merot; Bertrand	Volvic	N/A	N/A	FR
Benicourt; Claude	Houilles	N/A	N/A	FR
Cudrey; Claire	Gieres	N/A	N/A	FR

APPL-NO: 09/ 348930

DATE FILED: July 2, 1999

PARENT-CASE:

The present invention is a continuation of U.S. Ser. No. 08/945,321, filed Feb. 12, 1998, now abandoned, which was the national stage of PCT/FR96/00606, filed Apr. 19, 1996, which claims priority to FR9504754, filed Mar. 20, 1995.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	95/04754	April 20, 1995

US-CL-CURRENT: 800/295, 435/320.1 , 435/410 , 435/411 , 435/412 , 435/414 , 435/415 , 435/416 , 435/417 , 536/23.1 , 536/23.5 , 800/278 , 800/288 , 800/298 , 800/305 , 800/306 , 800/312 , 800/317 , 800/317.2 , 800/317.3 , 800/317.4 , 800/320 , 800/320.1 , 800/320.2 , 800/320.3 , 800/322

ABSTRACT:

The invention concerns the use of recombinant nucleotides sequences containing cDNA coding for a preduodenal lipase, or any sequence derived from this cDNA, for transforming plant cells in order to obtain recombinant preduodenal lipase or polypeptide derivatives.

The invention also concerns the use of genetically modified plants or parts thereof, or extracts of these plants or the use of recombinant preduodenal lipase or resultant polypeptide derivatives in the field of foodstuffs, or for producing medicaments, or in industry.

11 Claims, 8 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 8

---------- KWIC ---------

Detailed Description Text - DETX (135):

The plasmid pBIOC22 was digested totally by BglII and partly by HindIII in order to suppress the sequence which codes for the polypeptide Leu-Phe-Gly-Lys (first 4 amino acids) of the mature DGL protein. This sequence was replaced by that which codes for the signal peptide PS of 23 amino acids (ATG AAA GCC TTC ACA CTC GCT CTC TTC TTA GCT CTT TCC CTC TAT CTC CTG CCC AAT CCA GCC CAT TCC AGG
TTC AAT CCC ATC CGC CTC CCC ACC ACA CAC GAA CCC GCC) (SEQ ID NO: 17) fused to that of the first 4 codons of the sequence which codes for the mature DGL protein ("PPS-first 4 codons of mature DGL"). The **sequence "PPS**-first 4 codons for mature DGL" was **amplified** by PCR using the plasmid pMAT103 (Matsuoka and Nakamura, 1991) with the aid of the 2 following oligodeoxynucleotides 5' caggagatctgATG AAA GCC TTC ACA CTC GC 3'(SEQ ID NO: 15) and 5' ATG AAG CTT TCC AAA CAA GGA GGG TTC GTG TGT GGT TG 3' (SEQ ID NO: 18), in accordance with the protocol of PCR **amplification** described above in paragraph I. After double enzymatic digestion by BGIII and HindIII, the DNA fragments originating from the PCR **amplification** were purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium acetate, pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and then ligated to the plasmid DNA of pBIOC22, which had been doubly digested by BglII and HindIII, purified by electrophoresis over 0.8% agarose gel, electroeluted, subjected to precipitation with alcohol, dried and dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation was carried out with 100 ng of the dephosphorylated vector described above and 50 ng of the digested DNA fragments, originating from the PCR **amplification,** described above in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli Dh5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml of ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes.

US-PAT-NO: 6489100

DOCUMENT-IDENTIFIER: US 6489100 B1

TITLE: Microorganisms and methods for overproduction of DAHP by cloned PPS gene

DATE-ISSUED: December 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Liao; James C.	Los Angeles	CA	N/A	N/A

APPL-NO: 09/ 440503

DATE FILED: November 15, 1999

PARENT-CASE:

This is a request for filing a Continuation under 37 C.F.R. .sctn.1.60 of prior Ser. No. 08/801,454 filed on Feb. 18, 1997, now U.S. Pat. No. 5,906,925, and of prior Ser. No. 09/277,183 filed on Mar. 26, 1999, to be issued as U.S. Pat. No. 5,985,617, both of JAMES C. LIAO for MICROORGANISMS AND METHODS FOR OVERPRODUCTION OF DAHP BY CLONED PPS GENE.

US-CL-CURRENT: 435/6, 435/105 , 435/108 , 435/200 , 435/72 , 536/23.2 , 536/23.7 , 536/24.1

ABSTRACT:

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The **overexpression** of phosphoenol pyruvate synthase **increases** DAHP production to near theoretical yields.

10 Claims, 14 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Abstract Text - ABTX (1):

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom.

The **overexpression** of phosphoenol pyruvate synthase **increases** DAHP production to near theoretical yields.

Brief Summary Text - BSTX (18):

The present invention provides genetically engineered strains of microorganisms that **overexpress the pps gene for increasing** the production of DAHP to near theoretical yields. The present invention also provides genetically engineered strains of microorganisms where at least one of the plasmids pPS341, pPSL706, pPS706, or derivatives thereof is transformed into a microorganism for **increasing** the production of DAHP to near theoretical yields.

Brief Summary Text - BSTX (19):

The present invention further provides a method for **increasing** carbon flow for the biosynthesis of DAHP in a host cell comprising the steps of transforming into the host cell recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced levels relative to wild type host cells, concentrating the transformed cells through centrifugation, resuspending the cells in a minimal, nutrient lean medium, fermenting the resuspended cells, and isolating DAHP from the medium.

Brief Summary Text - BSTX (20):

The present invention further provides methods of **increasing** carbon flow into the common aromatic pathway of a host cell comprising the step of transforming the host cell with recombinant DNA comprising a **pps gene so that Pps** is expressed at appropriate point in the metabolic pathways at enhanced levels relative to wild type host cells.

Detailed Description Text - DETX (3):

The inventor have found that cell lines can be developed that **increase** the carbon flux into DAHP production and achieve near theoretical yields of DAHP by **overexpressing** phosphoenolpyruvate synthase (Pps) in the cell lines. **Overexpression** of Pps can **increase** the final concentration and yield of DAHP by as much as two-fold, to a near theoretical maximum as compared to wild type cell lines. The **overexpression** of Pps is achieved by transforming a cell line with recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced level relative to the wild type cell line and so that the yield of DAHP approaches its theoretical value.

Detailed Description Text - DETX (5):

Besides the use of the **pps gene,** the present invention also provides for transfer of genetic elements comprising the tkt gene, the gene coding for DAHP synthase (aroF in E. coli), the gene coding for 3-dehydroquinate synthase (arob in E. coli), or other genes encoding enzymes that catalyze reactions in the common aromatic pathway. Such a cell transformation can be achieved by transferring one or more plasmids that contain genes that code for enzymes that **increase** the carbon flux for DAHP synthesis and for subsequent synthesis of other desired cyclic, pre-aromatic, and aromatic metabolites. As a result of

this transfer of genetic element(s), more carbon enters and moves through the common aromatic pathway relative to wild type host cells not containing the genetic elements of the present invention.

Detailed Description Text - DETX (6):

In one embodiment, the present invention comprises a method for **increasing** carbon flow into the common aromatic pathway of a host cell by **increasing** the production of DAHP through the **overexpression** of Pps at the appropriate point in the common aromatic pathway to provide additional PEP at the point where PEP condenses with E4P. **Increasing** carbon flow requires the step of transforming the host cell with recombinant DNA containing a **pps gene so that Pps is overexpressed** at enhanced levels relative to wild type host cells. DAHP is then produced by fermentation of the transformed cell in a nutrient medium where the DAHP can be extracted from the medium on a batch wise or continuous extraction procedure.

Detailed Description Text - DETX (7):

In another embodiment, the present invention involves the co-**overexpression of a pps gene** and other genes coding for enzymes of the common aromatic pathway where additional genetic material is transformed into the host cell. The genes transferred can include the tkt gene, DAHP synthase gene and DHQ synthase gene (preferably the aroF or aroB genes, respectively). Although the work so far has centered around transforming certain host cell strains of E. coli such as AB2847 aroB, this particular host cell may not be the preferred host cells for the commercial production of DAHP or DAHP metabolites through the **overexpression** of Pps.

Detailed Description Text - DETX (8):

Another embodiment of the present invention is a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway. This method involves the step of **increasing** expression of Pps in the host cell relative to a wild type host cell. The step of **increasing** expression of Pps can include transferring into the host cell a vector carrying the **pps gene**. The **overexpression** of Pps results in forcing **increased** carbon flow into the biosynthesis of DAHP.

Detailed Description Text - DETX (9):

In another embodiment of the present invention, a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway relative to wild type host cell's biosynthetic production of such compound is provided. This method requires the step of **increasing** expression in a host cell of a protein catalyzing conversion of pyruvate to PEP. The expression of such a protein can involve transferring into the host cell recombinant DNA including a **pps gene**.

Detailed Description Text - DETX (55):

One preferred embodiment of the present invention encompasses modification

of a host cell to cause **overexpression** of an enzyme having the catalytic properties of naturally derived Pps, and, thereby maximizing the yield of DAHP to near theoretical yields. Enzymes having the catalytic activity of Pps include, but are not limited to, Pps produced by expression in whole cells of a naturally derived **pps gene,** enzymes produced by expression in whole cells of a naturally derived **pps gene** modified by sequence deletion or addition so that the expressed enzyme has an amino acid **sequence that varies from unmodified Pps,** abzymes produced to have catalytic sites with steric and electronic properties corresponding to catalytic sites of Pps, or other proteins produced to have the capability of catalyzing the conversion of pyruvate to PEP by any other art recognized means.

Detailed Description Text - DETX (57):

Additionally, the transformation of DNA, including the **pps gene,** into microorganisms engineered for the **overexpression** of other substrates, and/or **overexpression** or derepression of enzymes in the pentose phosphate or common aromatic pathway can be used to tailor the microorganism to achieve near theoretical yields of such DAHP metabolites as tyrosine, tryptophan, phenylalanine, and other aromatic metabolites such as indigo, catechol and quinoid organics such as quinic acid, benzoquinone, and hydroquinone.

Detailed Description Text - DETX (91):

This example demonstrates that the E. Coli AB2847 is unable to utilize DAHP, and accumulates DAHP in the medium if DAHP synthase is **overexpressed**. This strain was used as a host for detecting the flux committed to the aromatic pathways. Since Draths et al. (Draths, K. M., D. L. Pompliano, D. L. Conley, J. W. Frost, A. Berry, G. L. Disbrow, R. J. Staversky, and J. C. Lievense, "Biocatalytic synthesis of aromatics from D-glucose: The role of transketolase," J. Am. Chem. Soc., 1992, 114, 3956-3962) have shown a possible limitation in the production of DAHP by E4P, pATI (containing both aroG.sup.fbr and tktA) was transformed into AB2847 to eliminate the limitation of E4P. To test whether PEP supply limits DAHP production, PEP synthase (Pps) was **overexpressed** in AB2847/pAT1 by transforming plasmid pPS341 into this strain. 20-70 copies of the **pps gene** were expressed in the host cells. As a control, pPS341 was substituted by pPS341.times.1, which encodes an inactive, but stable **pps gene** product. The use of the inactive Pps control allowed discrimination between the effect of Pps activity and that of protein **overexpression**.

Detailed Description Text - DETX (97):

As shown above, Pps **overexpression** improved DAHP production from glucose. We were interested to know whether the basal level of Pps expression in glucose medium contributed to the production of DAHP. Therefore, the chromosomal **pps gene** in strain AB2847 was knocked out. The resulting strain (JCL1362) was used as the host to repeat the above experiments. Results show that inactivation of chromosomal pps did not significantly affect the DAHP production in strains containing pRW5 or pAT1 (FIG. 2B). Therefore, the basal level of pps expression in glucose medium did not contribute to the DAHP production.

Detailed Description Text - DETX (116):

Quinoid organics can be derived fromr dehydroquinate which is a down-stream metabolite of DAHP. To produce quinic acid, E. coli AB2848 aroD harboring pTW8090A which contains the gene qad (quinic acid dehydrogenase from Klebsiella pneuinoniae) (ref: Draths, Ward, and Frost, 1992, JACS, 114, 9725-9726), and pKD136 (ref: same as above) which contains tkt, aroF, and aroB genes can be used as a host. The **pps gene** can be cloned into one of these plasmids and be simultaneously **overexpressed**. It has been reported that at least 80 mM of D-glucose can be converted into 25 mM of quinic acid. After cell removal, quinic acid in the supernatant can be converted into benzoquinone after addition of sulfuric acid and technical grade manganese (IV) dioxide and heating at 100.degree. C. for 1 h. In the absence of acidification, aqueous solutions of purified quinic acid were converted. to hydroquinone in 10% yield upon heating at 100.degree. C. for 18 h with technical grade manganese dioxide.

Claims Text - CLTX (7):

7. A process for the production of DAHP which comprises cultivating a microorganism in a nutrient medium and **overexpressing the Pps gene**.

Claims Text - CLTX (8):

8. The process of claim 7 wherein the step of **overexpressing the Pps gene** comprises transforming a plasmid selected from the group consisting of pPS341, pPSL706, and pPS706 into the microorganism.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2003/06/17 14:01
2	L2	331546	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2003/06/17 14:02
3	L3	76345	promoter$1	USPAT; US-PGPUB	2003/06/17 14:02
4	L4	1383639	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2003/06/17 14:02
5	L5	60	2 near10 4 near10 3	USPAT; US-PGPUB	2003/06/17 14:03
6	L6	9302	pps or phosphoenol adj pyruvate adj synthase$1	USPAT; US-PGPUB	2003/06/17 14:29
7	L7	94	6 near4 (gene$1 or sequence$1)	USPAT; US-PGPUB	2003/06/17 14:29
8	L8	22	7 same (overexpress$ or amplif$10 or increas$8)	USPAT; US-PGPUB	2003/06/17 14:30
9	L9	17	7 and 2	USPAT; US-PGPUB	2003/06/17 14:48

PGPUB-DOCUMENT-NUMBER: 20030003573

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030003573 A1

TITLE: Hepatocytes for therapy and drug screening made from embryonic stem cells

PUBLICATION-DATE: January 2, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Rambhatle, Lakshmi	Redwood City	CA	US	
Carpenter, Melissa K.	Castro Valley	CA	US	

APPL-NO: 10/ 087142

DATE FILED: March 1, 2002

RELATED-US-APPL-DATA:

child 10087142 A1 20020301

parent continuation-in-part-of 10001267 20011031 US PENDING

child 10001267 20011031 US

parent continuation-in-part-of 09872182 20010531 US PENDING

non-provisional-of-provisional 60200095 20000427 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
US	PCT/US01/13471	2001US-PCT/US01/13471	April 26, 2001
WO	01/81549	2000WO-01/81549	November 1, 2000

US-CL-CURRENT: 435/366, 435/370

ABSTRACT:

It has been discovered that when pluripotent stem cells are cultured in the presence of a hepatocyte differentiation agent, a population of cells is derived that has a remarkably high proportion of cells with phenotypic characteristics of liver cells. In one example, human embryonic stem cells are allowed to form embryoid bodies, and then combined with the differentiation agent n-butyrate, optionally supplemented with maturation factors. In another example, n-butyrate is added to human embryonic stem cells in feeder-free culture. Either way, a remarkably uniform cell population is obtained, which is predominated by cells with morphological features of hepatocytes, expressing surface markers characteristic of hepatocytes, and having enzymatic and

biosynthetic activity important for liver function. Since stem cells readily proliferate in culture, this system provides an abundant source of cells of the hepatocyte lineage for a variety of applications, such as drug screening, and replenishing liver function in the context of clinical treatment.

REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of pending U.S. utility application 10/001,267, filed Oct. 31, 2001, which is a continuation-in-part of U.S. Ser. No. 09/872,182, filed May 31, 2001; and International Patent Application PCT/US01/13471, filed Apr. 26, 2001 (designating the U.S. and published as WO 01/81549 on Nov. 1, 2001); which in turn claims priority to U.S. provisional patent application No. 60/200,095, filed Apr. 27, 2000.

[0002] This application claims the priority benefit of all the aforelisted applications. The four priority documents are hereby incorporated herein by reference in their entirety, along with U.S. utility application 09/718,308, and International Patent Publication WO 01/51616.

---------- KWIC ---------

Detail Description Paragraph - DETX (107):

[0132] Matched hepatocyte lineage cells with allotypic differences can be obtained in the following fashion. pPS cells in feeder-free culture are genetically modified according to the techniques described in International Patent Publication WO 01/51616 (Geron Corp.). Modifications are made to a particular p450 component or other drug metabolizing enzyme to alter its function in a manner that makes it resemble a less frequent but naturally occurring allotype. For example, where the naturally occurring variant results in loss of expression or expression of a non-functional protein, then the corresponding **gene in pPS** cells can simply be modified to remove transcription or translation start signals. Where the natural allotype causes expression of mutant enzyme, then the corresponding **gene in pPS** cells can be replaced with the mutant form (either by replacing the endogenous gene, or inserting the mutant transgene elsewhere). Homologous recombination using an appropriate targeting vector can achieve any of these changes, but any suitable genetic manipulation technique can be used. The modification can be made in a heterozygous or homozygous fashion.

Detail Description Paragraph - DETX (164):

[0187] RT-PCR analysis of expression at the transcription level was conducted as follows: RNA was extracted from the cells using RNAeasy Kit.TM. (Qiagen) as per manufacturer's instructions. The final product was then digested with DNAse to get rid of contaminating genomic DNA. The RNA was incubated in RNA guard (Pharmacia Upjohn) and DNAse I (Pharmacia Upjohn) in buffer containing 10 mM Tris pH 7.5, 10 mM MgCl.sub.2, and 5 mM DDT at 37.degree. C. for 30-45 minutes. To remove protein from the sample, phenol chloroform extraction was performed and the RNA precipitated with 3 M sodium **acetate** and 100% cold ethanol. The RNA was washed with 70% ethanol, and the pellet was air-dried and resuspended in DEPC-treated water. For the reverse

transcriptase (RT) reaction, 500 ng of total RNA was combined with a final concentration of 1.times. First Strand Buffer (Gibco), 20 mM DDT and 25 .mu.g/mL random hexamers (Pharmacia Upjohn). The RNA was denatured for 10 min at 70.degree. C., followed by annealing at room temperature for 10 min. dNTPs were added at a final concentration of 1 mM along with 0.5 .mu.L of Superscript II RT (Gibco), incubated at 42.degree. C. for 50 minutes, and then heat-inactivated at 80.degree. C. for 10 min. Samples were then stored at -20.degree. C. till they were processed for PCR analysis. Standard polymerase chain reaction (PCR) was performed using primers specific for the markers of interest in the following reaction mixture: cDNA 1.0 .mu.L, 10.times.PCR buffer (Gibco) 2.5 .mu.L, 10.times.MgCl.sub.2 2.5 .mu.L, 2.5 mM dNTP 3.0 .mu.L, 5 .mu.M 3'-primer 1.0 .mu.L, 5 .mu.M 5'-primer, 1.0 .mu.L, Taq 0.4 .mu.L, DEPC-water 13.6 .mu.L. Selected markers and reaction conditions are shown in Table 3.

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TITLE: Method for producing hemin proteins using plant cells, resulting proteins and products containing same

PUBLICATION-DATE: December 19, 2002

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FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
FR	95/08615	1995FR-95/08615	July 17, 1995

US-CL-CURRENT: 800/288, 800/282

ABSTRACT:

A method for producing haemin proteins by (i) inserting into plant cells one or more nucleic acid molecules that each comprise at least one sequence coding for a protein component of an animal haemin protein capable of reversibly binding oxygen, or for a variant or portion of said protein component, and optionally a sequence coding for a selection agent; (ii) selecting cells containing nucleic

acid coding for the protein component of the haemin protein; (iii) optionally propagating the transformed cells either in a culture or by regenerating whole transgenic or chimeric plants; and (iv) recovering and optionally purifying a haemin protein that includes a complex consisting of the protein or proteins coded for by said nucleic acid and at least one iron-containing porphyritic nucleus, or a plurality of such complexes.

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Detail Description Paragraph - DETX (10):

[0130] The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml tetracycline, was extracted according to the alkaline lysis method (Birnboim and Doly, 1979) and analyzed by enzymatic digestion with restriction enzymes. Next, the HindIII restriction site of the plasmid DNA of the selected clone was modified at an EcoRI restriction site with the aid of a phosphorylated HindIII-EcoRI adaptor (Stratagene Cloning Systems). To carry out this modification, 500 ng of plasmid DNA of the selected clone were digested with HindIII, dephosphorylated with the enzyme calf intestinal alkaline phosphatase (Boeringer Mannheim) according to the manufacturer's recommendations and coprecipitated in the presence of 1500 ng of HindIII-EcoRI adaptor DNA, 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min. After centrifugation at 12000 g for 30 min, the precipitated DNA was washed with 70% ethanol, dried, taken up in 8 .mu.l of water, heated at 65.degree. C. for 10 min, and then ligated in the presence of 1 .mu.l of 10.times. T4 DNA ligase buffer (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. After inactivation of the T4 DNA ligase at 65.degree. C. for 10 min, the ligation reaction mixture was digested with EcoRI, purified by electrophoresis on a 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12000 g for 30 min, washed with 70% ethanol and then dried. The E. coli DH5.alpha. bacteria previously made competent were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml tetracycline was extracted according to the alkaline lysis method (Birnboim and Doly, 1979) and analyzed by enzymatic digestion with HindIII and EcoRI in particular. The resulting binary plasmid, which now possesses only the last 9 codons of the coding sequences of the cat gene and in which the EcoRI site is unique, was called pBIOC4.

Detail Description Paragraph - DETX (12):

[0132] The expression cassette, consisting of the pd35S promoter and the 35S polyA terminator, was isolated from the plasmid pJIT163D. The plasmid pJIT163D is derived from the plasmid pJIT163 which is itself derived from the plasmid pJIT60 (Guerineau and Mullineaux, 1993). The plasmid pJIT163 possesses an ATG codon between the HindIII and SalI sites of the polylinker. To eliminate this ATG and to obtain the plasmid pJIT163D, the plasmid DNA pJIT163 was doubly digested with HindIII and SalI, purified by electrophoresis on a 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12000 g for 30 min, washed with 70%

ethanol, dried, subjected to the action of the Klenow enzyme (New England Biolabs) according to the manufacturer's recommendations, deproteinized by extraction with 1 volume of phenol:chloroform:isoamyl alcohol (25:24:1) and then 1 volume of chloroform:isoamyl alcohol (24:1), precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12000 g for 30 min, washed with 70% ethanol, dried and finally ligated in the presence of 1 .mu.l of 10.times. T4 DNA ligase buffer (Amersham) and 2.5 U of T4 DNA ligase enzyme (Amersham) at 14.degree. C. for 16 hours. The E. coli DH5a bacteria previously made competent, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml ampicillin, was extracted according to the alkaline lysis method (Birnboim and Doly, 1979) and analyzed by enzymatic digestion with restriction enzymes. To isolate the expression cassette consisting of the pd35S promoter and of the 35S polyA terminator (SacI-XhoI fragment), the plasmid DNA of the pJIT163D clone selected was digested with SacI and XhoI. The SacI-XhoI-fragment, carrying the expression cassette, was purified by electrophoresis on a 0.8% agarose gel, electroeluted (Sambrook et al., 1989) precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12000 g for 30 min, washed with 70% ethanol, dried and then subjected to the action of Mung Bean nuclease enzyme (New England Biolabs) according to the manufacturer's recommendations. This purified insert (200 ng) was cloned into the plasmid DNA of pBIOC4 (20 ng) digested with EcoRI, treated with the Mung Bean nuclease enzyme and dephosphorylated with the enzyme calf intestinal alkaline phosphatase (Boehringer Mannheim) according to the manufacturer's recommendations. The ligation reaction was carried out in 20 .mu.l, in the presence of 2 .mu.l of 10.times. T4 DNA ligase buffer (Amersham), 2 .mu.l of 50% polyethylene glycol 8000 and 5 U of T4 DNA ligase enzyme (Amersham) at 14.degree. C. for 16 hours. The E. coli DH5.degree. C. bacteria previously made competent were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml tetracyclin was extracted according to the alkaline lysis method (Birnboim and Doly, 1979) and analyzed by enzymatic digestion with restriction enzymes. The resulting plasmid was called pBIOC21.

Detail Description Paragraph - DETX (15):

[0135] The co-expression binary plasmid is derived from pBIOC21. It contains two expression cassettes each consisting of a pd35S promoter and a 35S polyA terminator but differ in the polylinker separating the promoter from the terminator. One of the expression cassettes is that of pBIOC21 already described in paragraph I.a. The other expression cassette was obtained by replacing the HindIII-BamHI-SmaI-EcoRI polylinker of pJIT163D (described in paragraph I.a.) by a HindIII-EcoRI adaptor carrying the PacI, AscI, MluI and HpaI restriction sites. This adaptor was obtained by renaturation of the 2 oligodeoxynucleotides WD11 (5' AGC TGA TTA ATT AAG GCG CGC CAC GCG TTA AC 3') and WD12 (5' AAT TGT TAA CGC GTG GCG CGC CTT AAT TAA TC 3') which are complementary for their 28 terminal 3' nucleotides. One hundred .mu.M of each of these two oligodeoxynucleotides were previously phosphorylated by the action of 10 U of T4 polynucleotide kinase enzyme (New England Biolabs) in a total reaction volume of 10 .mu.l containing 1 .mu.l of 10.times. T4 polynucleotide kinase buffer (New England Biolabs) and 3 .mu.l of ATP (95 mM). The two reaction mixtures were incubated at 37.degree. C. for 1 hour, and then at

65.degree. C. for 20 min. They were then combined and their volume was adjusted to 500 .mu.l. After extraction with 1 volume of phenol:chloroform:isoamyl alcohol (25:24:1) and 1 volume of chloroform:isoamyl alcohol (24:1), 50 .mu.l of 3 M sodium **acetate** pH 6.0 were added. The reaction mixture was incubated at 80.degree. C. for 10 min and then cooled slowly to room temperature. The DNA was then precipitated in the presence of 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 14000 g at 4.degree. C. for 1 hour, washed with 70% ethanol, centrifuged at 14000 g at 4.degree. C. for 10 min, dried, taken up in 10 .mu.l of H2O. The HindIII-EcoRI DNA fragment was then cloned at the HindIII-EcoRI sites of the plasmid DNA pJIT163D previously dephosphorylated with the enzyme calf intestinal alkaline phosphatase (New England Biolabs) according to the manufacturer's recommendations. The ligation reaction was carried out in a reaction volume of 20 .mu.l in the presence of 1 U of T4 DNA ligase (Gibco-BRL) for a total DNA concentration of 8.5 nM with a vector/insert molar ratio of 1 and of 4 .mu.l of 5.times. T4 DNA ligase buffer (Gibco-BRL) at 25.degree. C. for 16 hours. The E. coli DH5.alpha. bacteria previously made competent were transformed (Hanahan, 1985). The plasmid DNA of the clones obtained, selected on 100 .mu.g/ml ampicillin, was extracted according to the alkaline lysis method (Stephen et al., 1990) and analyzed by enzymatic digestion. The resulting clone was called pBIOC42. Its validity was verified by sequencing with the aid of the "Sequenase Version 2.0 DNA Sequencing" kit marketed by United States Biochemical (USB) according to the dideoxynucleotides method (Sanger et al., 1977). The reaction conditions follow the manufacturer's recommendations except for the denaturation and hybridization. The reaction medium containing the plasmid DNA (0.5 to 1 pmol), the oligonucleotide primer (2 pmol), 10% DMSO and the lx reaction buffer (USB), is incubated at 100.degree. C. for 10 min, then suddenly cooled to -80.degree. C. in dry ice.

Detail Description Paragraph - DETX (26):

[0146] The third stage was the PCR amplification of the complete cDNA encoding the .alpha. globin chain (142 codons including the initiator ATG). The two types of DNA fragments amplified in the first and second stages served as template DNA and the two primers used were WD13 and WD14. The PCR amplification was carried out as described in the first stage except that the hybridization temperature of the cycle is 60.degree. C. The amplified DNA fragments were then extracted with H.sub.2O-saturated ether after having adjusted the volume to 500 .mu.l with TE buffer (10 mM Tris-HCl pH 8.0, 1 mM EDTA). After extraction with 1 volume of phenol:chloroform:isoamyl alcohol (25:24: 1) and 1 volume of chloroform:isoamyl alcohol (24: 1), the DNA fragments were precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 6.0 and 2 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 14000 g at 4.degree. C. for 30 min, washed with 70% ethanol, centrifuged at 14000 g at 4.degree. C. for 10 min, dried, taken up in 50 .mu.l of H.sub.2O. Next, 25 .mu.l of these DNA fragments were doubly digested with HindIII and EcoRI, purified by electrophoresis on 1.8% agarose gel and by the action of the "Geneclean 11" kit (BIO101) and cloned at the HindIII and EcoRI sites of the plasmid pNEB193 marketed by New England Biolabs, and previously dephosphorylated with the enzyme calf intestinal alkaline phosphatase (New England Biolabs) according to the manufacturer's recommendations. The ligation and the transformation were carried out as described in section I.b. The plasmid DNA of the clones obtained, selected on 100 .mu.g/ml ampicillin, was

extracted according to the alkaline lysis method (Stephen et al., 1990) and analyzed by enzymatic digestion. The resulting clone was called pBIOC44. The nucleotide sequence of the cDNA encoding the recombinant .alpha. globin chain was verified by sequencing with the aid of the "Sequenase Version 2.0 DNA Sequencing" kit marketed by United States Biochemical (USB) as described in section I.b. The sequencing revealed two silent mutations situated at the forty-eighth nucleotide (C modified to T) and at the fifty-fourth (T modified to C) of the coding sequence for the .alpha. globin chain.

Detail Description Paragraph - DETX (99):

[0219] To allow vacuolar targeting, the **sequence encoding the prepropeptide (PPS)** of sporamine A of the tuberized roots of sweet potato (Murakami et al., 1986; Matsuoka and Nakamura, 1991), which corresponds to the signal peptide followed by the N-terminal sequence for vacuolar targeting (ATG AAA GCC TTC ACA CTC GCT CTC TTC TTA GCT CTT TCC CTC TAT CTC CTG CCC AAT CCA GCC CAT TCC AGG TTC
AAT CCC ATC CGC CTC CCC ACC ACA CAC GAA CCC GCC), is fused with the first codon of the sequence encoding, on the one hand, the mature .alpha. globin chain (deletion of the initiator ATG) and, on the other hand, the mature .beta. globin chain (deletion of the initiator ATG) while maintaining the open reading frames. This prepropeptide of 37 amino acids was isolated from the plasmid pMAT103 (Matuoka and Nakamura, 1991) and used during the carrying out of the constructions.

US-PAT-NO: 6573431

DOCUMENT-IDENTIFIER: US 6573431 B1

TITLE: Recombinant preduodenal lipases and polypeptides derivatives produced by plants, processes for obtaining them and their uses

DATE-ISSUED: June 3, 2003

INVENTOR-INFORMATION:

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APPL-NO: 09/ 348930

DATE FILED: July 2, 1999

PARENT-CASE:

The present invention is a continuation of U.S. Ser. No. 08/945,321, filed Feb. 12, 1998, now abandoned, which was the national stage of PCT/FR96/00606, filed Apr. 19, 1996, which claims priority to FR9504754, filed Mar. 20, 1995.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	95/04754	April 20, 1995

US-CL-CURRENT: 800/295, 435/320.1 , 435/410 , 435/411 , 435/412 , 435/414 , 435/415 , 435/416 , 435/417 , 536/23.1 , 536/23.5 , 800/278 , 800/288 , 800/298 , 800/305 , 800/306 , 800/312 , 800/317 , 800/317.2 , 800/317.3 , 800/317.4 , 800/320 , 800/320.1 , 800/320.2 , 800/320.3 , 800/322

ABSTRACT:

The invention concerns the use of recombinant nucleotides sequences containing cDNA coding for a preduodenal lipase, or any sequence derived from this cDNA, for transforming plant cells in order to obtain recombinant preduodenal lipase or polypeptide derivatives.

The invention also concerns the use of genetically modified plants or parts thereof, or extracts of these plants or the use of recombinant preduodenal lipase or resultant polypeptide derivatives in the field of foodstuffs, or for producing medicaments, or in industry.

11 Claims, 8 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 8

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Detailed Description Text - DETX (44):
The invention more particularly relates to a process for the preparation of the abovementioned recombinant DGL and/or polypeptide (.DELTA.54) and/or polypeptide (.DELTA.4), characterized in that it comprises: transformation of explant cells of a plant (in particular explants of leaves) by bringing the latter together with a strain of Agrobacterium tumefaciens transformed by a plasmid as described above containing the recombinant nucleotide sequence pd35S-PS-DGL and/or the **sequence pd35S-PPS**-DGL, selection of the transformed explants on a medium containing kanamycin, production of transformed plants from the abovementioned transformed explants by culture of the latter on suitable media, extraction of the recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4), in particular by grinding the leaves and/or the seeds and/or the fruits of the abovementioned transformed plants in a suitable buffer, centrifugation and recovery of the supernatant constituting the plant extract of enzymatic activity, where appropriate, purification of the recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4) from the extract obtained during the preceding stage, in particular by chromatography carried out on the supernatant, which leads to the preparation of the recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4) in an essentially pure form.

Detailed Description Text - DETX (47):
The invention more particularly relates to a process for the preparation of recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4), characterized in that it comprises: transformation of explant cells of a plant by bringing the latter together with a strain of Agrobacterium tumefaciens transformed by a plasmid as described above containing the recombinant nucleotide **sequence pCRU-PPS-DGL and/or the sequence** pCRU-PS-DGL and/or the sequence pGEA1-RGLSP-DGL and/or the sequence pGEA6-RGLSP-DGL and/or the sequence pAR-IAR-RGLSP-DGL and/or the sequence p.gamma.zeine-RGLSP-DGL and/or the sequence p.gamma.zeine-RGLSP-DGL-KDEL, selection of the transformed explants on a medium containing kanamycin, production of transformed plants from the abovementioned transformed explants by culture of the latter on suitable media, extraction of the recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4), in particular by grinding seeds produced by the abovementioned transformed plants in a suitable buffer, centrifuging and recovering the supernatant containing the plant extract of enzymatic activity, where appropriate, purification of the recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4) from the extract obtained during the preceding stage, in particular by chromatography carried out on the supernatant, which leads to the preparation of the

recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4) in an essentially pure form.

Detailed Description Text - DETX (63):

The invention more particularly relates to the following plant extracts of enzymatic activity: the extracts of leaves and/or fruits and/or seeds of plants obtained by transformation of explant cells of these plants with the sequence pd35S-RGLSP-DGL or the sequence pd35S-PS-DGL or the **sequence pd35S-PPS**-DGL, according to one of the processes described above, and containing the recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4), in particular: the extract of tobacco leaves obtained by transformation of explant cells of tobacco leaves with the sequence pd35S-PS-DGL or the **sequence pd35S-PPS**-DGL, according to the process described above, and containing the polypeptide (.DELTA.54) in combination with the polypeptide (.DELTA.4), the percentage by weight by the mixture of these two polypeptides with respect to the total weight of proteins present in the said extract being from about 0.1 to about 20%, the enzymatic activity of the said extract being from about 100 U/g of FW to about 300 U/g of FW, the extract of tomato leaves or fruits obtained by transformation of explant cells of tomato leaves with the sequence pd35S-PS-DGL, or the **sequence pd35S-PPS**-DGL, according to the process described above, and containing the polypeptide (.DELTA.54) in combination with the polypeptide (.DELTA.4), the percentage by weight of this mixture of two polypeptides with respect to the total weight of proteins present in the said extract being from about 0.1% to about 20%, the enzymatic activity of the said extract being from about 100 U/g of FW to about 300 U/g of FW, the extract of tobacco leaves obtained by transformation of explant cells of tobacco leaves with the sequence pd35S-RGLSP-DGL, according to the process described above, and containing the polypeptide (.DELTA.4), the percentage by weight of this polypeptide with respect to the total weight of proteins present in the said extract being from about 0.1% to about 20%, the enzymatic activity of the said extract being from about 100 U/g of FW to about 300 U/g of FW, the extract of tobacco seeds obtained by transformation of explant cells of tobacco leaves with the sequence pd35S-PS-DGL or the **sequence pd35S-PPS**-DGL, according to the process described above, and containing the polypeptide (.DELTA.54), the percentage by weight of the polypeptide (.DELTA.54) with respect to the total weight of proteins present in the said extract being from about 0.1% to about 1%, the enzymatic activity of the said extract being from about 10 U/g of FW to about 300 U/g of FW, the extracts of plant seeds obtained by transformation of explant cells of these plants with the sequence pCRU-PS-DGL or the **sequence pCRU-PPS-DGL, or the sequence** pGEA1-RGLSP-DGL, or the sequence pGEA6-RGLSP-DGL,
according to one of the processes described above, and containing the recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4), in particular: the extract of rape seeds obtained by transformation of explant cells of rape leaves with the sequence pCRU-PS-DGL or the **sequence pCRU-PPS-DGL, or the sequence** pGEA1-RGLSP-DGL, or the sequence pGEA6-RGLSP-DGL,
according to the process described above, and containing the polypeptide (.DELTA.54), the percentage by weight of polypeptide (.DELTA.54) with respect to the total weight of proteins present in the said extract being from about 0.1% to about 1%, the enzymatic activity of the said extract being from about 10 U/g of FW to about 1,000 U/g of FW, the extracts of plant seeds obtained by

transformation of explant cells of these plants with the sequence pAR-IAR-RGLSP-DGL and/or the sequence p.gamma.zeine-RGLSP-DGL, and/or the sequence p.gamma.zeine-RGLSP-DGL-KDEL, according to one of the processes described above, and containing the recombinant DGL and/or the polypeptide (.DELTA.54) and/or the polypeptide (.DELTA.4), in particular: the extract of corn seeds obtained by transformation of explant cells of rape leaves with the sequence pAR-IAR-RGLSP-DGL and/or the sequence p.gamma.zeine-RGLSP-DGL, and/or the sequence p.gamma.zeine-RGLSP-DGL-KDEL, according to the process described above, and containing the polypeptide (.DELTA.54), the percentage by weight of polypeptide (.DELTA.54) with respect to the total weight of proteins present in the said extract being from about 0.1% to about 1%, the enzymatic activity of the said extract being from about 10 U/g of FW to about 1,000 U/g of FW.

Detailed Description Text - DETX (69):

The invention also relates to the polypeptide (.DELTA.54) and the polypeptide (.DELTA.4) obtained by purification of the enzymatic extract of plant leaves and/or seeds and/or fruits, notably solanaceae, such as transformed tobacco or tomato, themselves obtained from plant cells transformed with the sequence pd35S-PS-DGL or the **sequence pd35S-PPS-DGL, or the sequence** pd35S-RGLSP-DGL, according to the process described above, the said recombinant polypeptides (.DELTA.54) and (.DELTA.4) having a lipase activity as described above.

Detailed Description Text - DETX (70):

The invention also relates to the polypeptide (.DELTA.54) obtained by purification of the enzymatic extract of tobacco seeds, or that of rape seeds, these seeds originating, respectively, from transformed tobacco or rape plants, themselves obtained, respectively, from tobacco or rape cells transformed with the sequence pCRU-PS-DGL or the **sequence pCRU-PPS**-DGL, according to the processes described above, the recombinant polypeptide (.DELTA.54) having a lipase activity as described above.

Detailed Description Text - DETX (128):

The structural promoter of the nos gene which codes for nopaline synthase (Depicker et al., 1982), the sequence which codes for the nptII gene which codes for neomycin phosphotransferase II (Berg and Berg, 1983) deleted from the region of the first 8 codons, of which the initiator codon is methionine ATG, and fused to the sequence of the first 14 codons of the sequence which codes for the nos gene (Depicker et al., 1982), the sequence which codes for the nos gene devoid of the region of the first 14 codons, the nos terminator (Depicker et al., 1982), a region containing multiple cloning sites (also called polylinker) (HindIII-XbaI-SacI-HpaI-KpnI-ClaI-BglII) preceding the cat gene which codes for chloramphenicol acetyltransferase (Close and Rodriguez, 1982) and the terminal sequences of the gene 6 of the plasmid pTiA6 of Agrobacterium tumefaciens (Liu et al., 1993). To eliminate virtually all the sequence which codes for the cat gene, the plasmid pGA492 was digested twice by SacI (restriction site of the polylinker) and by ScaI (restriction site present in the sequence of the cat gene) and then subjected to the action of the enzyme T4 DNA polymerase (New England Biolabs) in accordance with the manufacturer's instructions. The ligation of the modified plasmid (ng) was carried out in a

reaction medium of 10 .mu.l comprising 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham); 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml of tetracycline, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The HindIII restriction site of the plasmid DNA of the clone retained was then modified into an EcoRI restriction site with the aid-of an phosphorylated HindIII-EcoRI adaptor (Stratagene Cloning Systems). To carry out this modification, 500 ng of plasmid DNA of the clone retained were digested by HindIII, dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions and coprecipitated in the presence of 1,500 ng of the HindIII-EcoRI DNA adaptor, 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of to absolute ethanol at -80.degree. C. for min. After centrifugation at 12,000 g for min, the DNA precipitated was washed with 70% ethanol, dried, taken up in 8 .mu.l of water, kept at 65.degree. C. for min and then ligated in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. After inactivation of the T4 DNA ligase at 65.degree. C. for min, the ligation reaction mixture was digested by EcoRI, purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C. for min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and then ligated as described above. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml of tetracycline, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by HindIII and EcoRI in particular. The resulting binary plasmid, which only has the last 9 codons of the sequence which codes for the cat gene and of which the EcoRI site is unique, was called pBIOC4.

Detailed Description Text - DETX (129):

The expression cassette made up of the promoter pd35S and the terminator polyA 35S was isolated using the plasmid pJIT163.DELTA.. The plasmid pJIT163.DELTA. is derived from the plasmid pJIT163, which itself is derived from the plasmid pJIT60 (Guerineau and Mullineaux, 1993). The plasmid pJIT163 possesses an ATG codon between the HindIII and SalI sites of the polylinker. To suppress this ATG and to obtain the plasmid pJIT163.DELTA., the plasmid pJIT163 DNA was digested twice by HindIII and SalI, purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C for min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried, subjected to the action of Klenow enzyme (New England Biolabs) in accordance with the manufacturer's instructions, deproteinated by extraction with 1 volume of phenol:chloroform:isoamyl alcohol (25:24:1) and then 1 volume of chloroform:isoamyl alcohol (24:1), precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C for 30 min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and, finally, ligated in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme

T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml of ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. To isolate the expression cassette made up of the promoter pd35S and the terminator polyA 35S (SacI-XhoI fragment), the plasmid DNA of the clone pJIT163.DELTA. retained was digested by SacI and XhoI. The SacI-XhoI fragment, carrying the expression cassette, was purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and then subjected to the action of Mung Bean Nuclease enzyme (New England Biolabs) in accordance with the manufacturer's instructions. This purified insert (200 ng) was cloned in the plasmid DNA of pBIOC4 (20 ng), which had been digested by EcoRI, treated with the enzyme Mung Bean Nuclease and dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation reaction was carried out in 20 .mu.l in the presence of 2 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham), 2 .mu.l of 50% polyethylene glycol 8000 and 5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli Dh5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 12 .mu.l/ml of tetracycline, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The resulting plasmid was called pBIOC21.

Detailed Description Text - DETX (130):

Dog gastric lipase (DGL) is synthesized naturally in the form of a precursor. The mature DGL protein is made up of 379 amino acids. The complementary DNA of DGL was cloned at the BglII and SalI sites of the expression vector pRU303, leading to the vector pDGL5.303 described in the international application no. WO 94/13816. It was used for construction of the binary plasmids pBIOC25, containing PS-DGL, and pBIOC26, containing **PPS-DGL, where the sequence** which codes for the mature DGL is preceded by that which codes for a signal peptide (PS) or a prepropeptide (PPS, that is to say a signal peptide followed by N-terminal vacuole-directing sequences) of plant origin respectively. The PS and **PPS sequences,** made up, respectively, of 23 and 37 amino acids, are those of a reserve protein of the tuberous roots of the sweet potato: sporamin A (Murakami et al., 1986; Matsukoa and Nakamura, 1991).

Detailed Description Text - DETX (131):

To simplify fusions between the sequence of mature DGL and that of the directing signals, PS or PPS, the plasmid pDGL5.303 was modified by introduction of a supplementary HindIII restriction site into the fourth and fifth codons of the mature DGL sequence by mutagenesis directed by PCR using 2 oligodeoxynucleotides, 5' caggagatc TTG TTT GGA AAG CTT CAT CCC 3'(SEQ ID NO: 10) (containing the unique BglII site in the plasmid and providing the supplementary HindIII site) and 5' CAT ATT CCT CAG CTG GGT ATC 3'(SEQ ID NO: 11) (containing the unique PvuII site in the plasmid). Amplification of the

BglII-PvuII fragment by PCR was carried out in 100 .mu.l of reaction medium comprising 10 .mu.l of the buffer Taq DNA polymerase.times.10 (500 mM KCl, 100 mM Tris-HCl, pH 9.0, and 1% Triton.times.100), 6 .mu.l of 25 mM MgCl.sub.2, 3 .mu.l of 10 mM dNTP (dATP, dCTP, dGTP and dTTP), 100 pM of each of the 2 oligodeoxynucleotides described above, 5 ng of matrix DNA (expression vector pRU303 including the complementary DNA of DGL), 2.5 U of Taq DNA polymerase (Promega) and 2 drops of vaseline oil. The DNA was denatured at 94.degree. C. for 30 min, subjected to 30 cycles, each of 1 min of denaturation at 94.degree. C., 1 min of hybridization at 50.degree. C. and 1 min of elongation at 72.degree. C., and then elongation at 72.degree. C. was continued for min. This PCR reaction was carried out in the "DNA Thermal Cycler" machine of PERKIN ELMER CETUS. The oil was removed by extraction with chloroform. The DNA fragments contained in the reaction medium were then precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and digested by the 2 restriction enzymes BglII and PvuII. The digested DNA fragments originating from the PCR were purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and then ligated to the plasmid DNA of the vector pDGL5.303, which had been digested twice by BglII and PvuII, purified by electrophoresis over 0.8% agarose gel, electroeluted, subjected to precipitation in alcohol, dried and dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation was carried out with 100 ng of the dephosphorylated vector described above and 50 ng of the digested DNA fragments, originating from the amplification by PCR, described above in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli Dh5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml of ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The plasmid DNA of some of the clones retained was verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). Introduction of this HindIII restriction site does not modify the genetic code of the DGL. In fact, the natural DGL sequence AAA TTA (Lys-Leu) becomes AAG CTT (Lys-Leu). The resulting plasmid was called pBIOC22 and includes the sequence of the mature DGL protein corresponding to:

Detailed Description Text - DETX (133):

The plasmid pBIOC22 was digested totally by BglII and partly by HindIII in order to suppress the sequence which codes for the polypeptide Leu-Phe-Gly-Lys (first 4 amino acids) of the mature DGL protein. This sequence was replaced by that which codes for the signal peptide PS of 23 amino acids (ATG AAA GCC TTC ACA CTC GCT CTC TTC TTA GCT CTT TCC CTC TAT CTC CTG CCC AAT CCA GCC CAT TCC)
(SEQ ID NO: 14) fused to that of the first 4 codons of the sequence which codes for the mature DGL protein ("PS-first 4 codons of mature DGL"). The sequence

"PS-first 4 codons for mature DGL" was amplified by PCR using the plasmid pMAT103 (Matsuoka and Nakamura, 1991) with the aid of the 2 following oligodeoxynucleotides 5' caggagatctgATG AAA GCC TTC ACA CTC GC 3'(SEQ ID NO: 15) and 5' ATG AAG CTT TCC AAA CAA GGA ATG GGC TGG ATT GGG CAG G 3'(SEQ ID NO:
16), in accordance with the protocol of PCR amplification described above in paragraph I. After double enzymatic digestion by BGIII and HindIII, the DNA fragments originating from the PCR amplification were purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and then ligated to the plasmid DNA of pBIOC22, which had been doubly digested by BglII and HindIII, purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), subjected to precipitation with alcohol, dried and dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation was carried out with 100 ng of the dephosphorylated vector described above and 50 ng of the digested DNA fragments, originating from the PCR amplification, described above in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml of ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The plasmid DNA of some of the clones retained was verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The sequences of the PS and the mature DGL were cloned, maintaining their open-reading frames. The cleavage sequence between the sequences of the PS and the mature DGL is Ser-Leu. The resulting plasmid was called pBIOC23. Starting from pBIOC23, the BglII-XbaI fragment carrying the sequence of PS-DGL was isolated by double enzymatic digestion by BglII and XbaI, purification by electrophoresis over 0.8% agarose gel, electroelution (Sambrook et al., 1989), precipitation with alcohol and drying. This DNA fragment was then treated with Klenow enzyme in accordance with the manufacturer's instructions and ligated to the plasmid DNA of pBIOC21, which had been digested at the HindIII site, treated with Klenow and dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation was carried out with 20 ng of the dephosphorylated vector described above and 200 ng of DNA fragments, containing the PS-DGL, described above in a reaction medium of 20 .mu.l in the presence of 2 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham), 2 .mu.l of 50% polyethylene glycol 8000 and 5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml of tetracycline, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The resulting clone was called pBIOC25. The nucleotide sequence of the fragment which codes for the recombinant protein PS-DGL was verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The plasmid DNA of the

binary vector pBIOC25 was introduced by direct transformation into the strain LBA4404 of Agrobacterium tumefaciens in accordance with the process of Holsters et al. (1978). The validity of the clone retained was verified by enzymatic digestion of the plasmid DNA introduced.

Detailed Description Text - DETX (135):

The plasmid pBIOC22 was digested totally by BglII and partly by HindIII in order to suppress the sequence which codes for the polypeptide Leu-Phe-Gly-Lys (first 4 amino acids) of the mature DGL protein. This sequence was replaced by that which codes for the signal peptide PS of 23 amino acids (ATG AAA GCC TTC ACA CTC GCT CTC TTC TTA GCT CTT TCC CTC TAT CTC CTG CCC AAT CCA GCC CAT TCC AGG
TTC AAT CCC ATC CGC CTC CCC ACC ACA CAC GAA CCC GCC) (SEQ ID NO: 17) fused to that of the first 4 codons of the sequence which codes for the mature DGL protein ("PPS-first 4 codons of mature DGL"). The **sequence "PPS**-first 4 codons for mature DGL" was amplified by PCR using the plasmid pMAT103 (Matsuoka and Nakamura, 1991) with the aid of the 2 following oligodeoxynucleotides 5' caggagatctgATG AAA GCC TTC ACA CTC GC 3'(SEQ ID NO: 15) and 5' ATG AAG CTT TCC AAA CAA GGA GGG TTC GTG TGT GGT TG 3' (SEQ ID NO: 18), in accordance with the protocol of PCR amplification described above in paragraph I. After double enzymatic digestion by BGIII and HindIII, the DNA fragments originating from the PCR amplification were purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and then ligated to the plasmid DNA of pBIOC22, which had been doubly digested by BglII and HindIII, purified by electrophoresis over 0.8% agarose gel, electroeluted, subjected to precipitation with alcohol, dried and dephosphorylated by the alkaline phosphatase enzyme of the intestihe of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation was carried out with 100 ng of the dephosphorylated vector described above and 50 ng of the digested DNA fragments, originating from the PCR amplification, described above in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli Dh5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml of ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes.

Detailed Description Text - DETX (136):

The plasmid DNA of some of the clones retained was verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The **sequences of the PPS** and the mature DGL were cloned, maintaining their open-reading frames. The cleavage sequence between the two sequences is Ala-Leu. The resulting plasmid was called pBIOC24. Starting from pBIOC24, the BglII-XbaI fragment carrying the **sequence of PPS**-DGL was isolated by double enzymatic digestion by BglII and XbaI, purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated with alcohol and dried. This DNA

fragment was then treated with Klenow enzyme in accordance with the manufacturer's instructions and ligated to the plasmid DNA of pBIOC21, which had been digested at the HindIII site, treated with Klenow and dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation was carried out with 20 ng of the dephosphorylated vector described above and 200 ng of DNA fragments, containing the PPS-DGL, described above in a reaction medium of 20 .mu.l in the presence of 2 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham), 2 .mu.l of 50% polyethylene glycol 8000 and 5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml of tetracycline, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The resulting clone was called pBIOC26. The nucleotide sequence of the fragment which codes for the recombinant protein PPS-DGL was verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The plasmid DNA of the binary vector pBIOC26 was introduced by direct transformation into the strain LBA4404 of Agrobacterium tumefaciens in accordance with the process of Holsters et al. (1978). The validity of the clone obtained was verified by enzymatic digestion of the plasmid DNA introduced.

Detailed Description Text - DETX (139):

Alignment of the polypeptide sequences of dog gastric lipase and of the precursor of rabbit gastric lipase has demonstrated that the sequence LFGK is present in the two proteins. In the polypeptide sequence of the rabbit lipase determined from the purified natural protein (Moreau et al., 1988), the first three residues L, F and G are absent and form part of the signal peptide of 22 amino acids of RGL. As a result, the signal peptide of rabbit gastric lipase devoid of these three common amino acids was fused to the mature protein sequence of dog gastric lipase. Its polypeptide sequence is made up of the following 19 amino acids: MWVLFMVAALLSALGTTHG (SEQ ID NO: 19). The plasmid pBIOC22 was thus digested totally by BhlII and partly by HindIII in order to suppress the sequence which codes for the polypeptide Leu-Phe-Gly-Lys (first 4 amino acids) of the mature DGL protein. This sequence was replaced by that which codes for the signal peptide RGLSP of rabbit gastric lipase of 19 amino acids (ATG TGG GTG CTT TTC ATG GTG GCA GCT TTG CTA TCT GCA CTT GGA ACTACA CAT
GGT) (SEQ ID NO: 20) fused to that of the first 4 codons of the mature DGL protein ("RGLSP-first 4 codons of mature DGL"). The sequence "RGLSP-first 4 codons of mature DGL" was amplified by PCR using the plasmid pJO101 with the aid of the 2 following oligodeoxynucleotides 5' aggagatctcaacaATG TGG GTG CTT TTC ATG GTG 3' (SEQ ID NO: 21) and 5' G ATG AAG CTT TCC AAA CAA ACC ATG TGT AGT
TCC AAG TG 3' (SEQ ID NO: 22), in accordance with the protocol of PCR amplification described above in paragraph I. After double enzymatic digestion by BGlII and HindIII, the DNA fragments originating from the PCR amplification were purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and

then ligated to the plasmid DNA of pBIOC22, which had been doubly digested by BglII and HindIII, purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), subjected to precipitation with alcohol, dried and dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation was carried out with 100 ng of the dephosphorylated vector described above and 50 ng of the digested DNA fragments, originating from the PCR amplification, described above in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on a medium containing 50 .mu.g/ml of ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The plasmid DNA of some of the clones retained was verified by sequencing with the aid of the T.sub.7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The sequences of the RGLSP and the mature DGL were cloned, maintaining their open reading frames (that is to say such that they constitute a unique open reading frame). The cleavage sequence between the sequences of the RGLSP and the mature DGL is Gly-Leu. The resulting plasmid was called pBIOC40. Starting from pBIOC40, the BglII-XbaI fragment carrying the sequence of RGLSPS-DGL was isolated by double enzymatic digestion by BglII and XbaI, purification by electrophoresis over 0.8% agarose gel, electroelution (Sambrook et al., 1989), precipitation with alcohol and drying. This DNA fragment was then treated with Klenow enzyme in accordance with the manufacturer's instructions and ligated to the plasmid DNA of pBIOC21, which had been digested at the HindIII site, treated with Klenow and dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation was carried out with 20 ng of the dephosphorylated vector described above and 200 ng of DNA fragments, containing the RGLSP-DGL, described above in a reaction medium of 20 .mu.l in the presence of 2 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham), 2 .mu.l of 50% polyethylene glycol 8000 and 5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on a medium containing 12 .mu.g/ml of tetracycline, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The resulting clone was called pBIOC41. The nucleotide sequence of the fragments which code for the recombinant protein RGLSP-DGL was verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The plasmid DNA of the binary vector pBIOC41 was introduced by direct transformation into the strain LBA4404 of Agrobacterium tumefaciens in accordance with the process of Holsters et al. (1978). The validity of the clone retained was verified by enzymatic digestion of the plasmid DNA introduced.

Detailed Description Text - DETX (149):

Isolation of the BglII-XbaI fragment carrying the **sequence PPS**-DGL using pBIOC24 has already been described in I-A-b. This fragment was ligated to the plasmid DNA of pBIOC28 at the EcoRI site treated with Klenow and

dephosphorylated by the alkaline phosphatase enzyme of the intestine of the calf (Boehringer Mannheim) in accordance with the manufacturer's instructions. The ligation was carried out with 20 ng of the dephosphorylated vector described above and 200 ng of the DNA fragments BglII-XbaI containing PPS-DGL in a reaction medium of 20 .mu.l in the presence of the buffer T4 DNA ligase.times.10 (Amersham), 2 .mu.l of 50% polyethylene glycol 8000 and 5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on a medium containing 12 .mu.l/ml of tetracycline, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The resulting plasmid was called pBIOC29. The nucleotide **sequence of the recombinant protein PPS**-DGL was verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The plasmid DNA of the binary vector pBIOC29 was introduced by direct transformation into the strain LBA4404 of Agrobacterium tumefaciens in accordance with the process of Holsters et al. (1978). The validity of the clone retained was verified by enzymatic digestion of the plasmid DNA introduced.

Detailed Description Text - DETX (153):

To obtain the binary plasmid pBIOC90 similar to pBIOC21 but in which the promoter pd35S was replaced by the promoter pGEA1D, the fragment HindIII-BamHI treated with Klenow, containing the promoter pGEA1, was isolated using plasmid pGUS2-pGEA1. The clone pGUS-2-pGEA1deriving from pBI221 by replacement of the promoter p35S by the promoter pGEA1, contains 2 ATG in frame: ATG of the gene GEA1 (Em2) and ATG of the gene gus. The ATG of the gene GEA1 was destroyed. The DNA fragment contained between the SalI site and the sequences upstream from the ATG of the gene GEA1 of the clone pGUS-2-pGEA1 was then amplified by PCR using 2 oligonucleotides: 5' CAAACGTGTACAATAGCCC 3' (SEQ ID NO: 23) and 5' CCCGGGGATCCTTTTTTG 3' (SEQ ID NO: 24). The hybridization temperature was adjusted. The fragment amplified by PCR was digested by SalI and BamHI, purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al. 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for minutes, centrifuged at 12000 g for 30 minutes, washed with 70% ethanol, then ligated to plasmid DNA of pGUS-2-GEA1 double digested by SalI and BamHI, purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), subjected to precipitation with alcohol, dried. Ligation was carried out with 100 ng of vector and 50 ng of digested DNA fragments originating from the PCR amplification described above, in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli Dh5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. Certain retained clones were verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The resulting clone was called pGUS-2-pGEA1D.

Detailed Description Text - DETX (161):

The fragment amplified by PCR was digested by AccI and BamHI, purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al. 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 minutes, centrifuged at 12000 g for 30 minutes, washed with 70% ethanol, dried, then ligated to plasmid DNA of pGUS-2-GEA6 double digested by AccI and BamHI, purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), subjected to precipitation with alcohol, dried. Ligation was carried out with 100 ng of the vector described above and 50 ng of digested DNA fragments originating from the PCR amplification described above, in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli Dh5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. Certain retained clones were verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The resulting clone was called pGUS-2-pGEA6D.

Detailed Description Text - DETX (175):

The sequence which codes for the precursor of HGL was isolated by double digestion with PstI and DraI, purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at minus 80.degree. C. for minutes, centrifuged at 12000 g for 30 minutes, washed with 70% ethanol and dried. Then, it was cloned at the PstI and SpeI sites (subjected to the action of the enzyme T4 DNA polymerase (Biolabs) in accordance with the manufacturer's instructions) of the plasmid pBSIISK+ marketed by Stratagene. The ligation was carried out with 100 ng of the vector and 50 ng of the DNA fragments carrying the sequence which codes for the precursor of HGL described above, in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli DH5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml of ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. The resulting plasmid was called pBIOC83.

Detailed Description Text - DETX (177):

The PCR amplification of the fragment PstI-MscI was carried out in 100 .mu.l of reaction medium containing 10 .mu.l of the buffer Taq DNA polymerase.times.10 (500 mM KCl, 100 mM Tris-HCl, pH 9.0 and 1% Triton.times.100), 6 .mu.l of mM MgCl.sub.2, 3 .mu.l of 10 mM dNTP (dATP, dCTP, dGTP and dTTP) , 100 pM of each of the 2 oligodeoxy-nucleotides described above, 5 ng of matrix DNA (vector pBIOC83), 2.5 U of Tag DNA polymerase (Promega) and 2 drops of vaseline oil. The DNA was denatured at 94.degree. C. for 5 minutes, subjected to 30 cycles each constituted by 1 minute of

denaturation at 94.degree. C., 1 minute of hybridization at 65.degree. C. and 1 minute of elongation at 72.degree. C., then elongation at 72.degree. C. was continued for 5 minutes. This PCR reaction was carried out in the "DNA Thermal Cycler" machine of PERKIN ELMER CETUS. The oil was removed by extraction with chloroform. The DNA fragments contained in the reaction medium were then precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at minus 80.degree. C. for 30 min, centrifuged at 12,000 g for 30 min, washed with 70% ethanol, dried and digested by the 2 restriction enzymes PstI and MscI. The digested DNA fragments originating from the PCR amplification were purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate,** pH 4.8, and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12,000 g for min., washed with 70% ethanol, dried and then ligated to the plasmid DNA of pBIOC83, which had been digested twice by PstI and MscI, purified by electrophoresis over 0.8% agarose gel, electroeluted, subjected to precipitation with alcohol, dried. The ligation was carried out with 100 ng of the vector and 50 ng of the digested DNA fragments, originating from the amplification by PCR, described above, in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli Dh5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml of ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. Some of the retained clones were verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). Introduction of the BamHI restriction site does not modify the genetic code of the HGL. In fact, the natural HGL sequence GGA AGC (Gly-Ser) becomes GGA TCC (Gly-Ser). The resulting plasmid was called pBIOC84.

Detailed Description Text - DETX (181):

The plasmid pBIOC84 was digested twice by PstI and BamHI in order to suppress the sequence which codes for the signal peptide HSLSP and the first 8 amino acids of the mature HGL protein (Leu-Phe-Gly-Lys-Leu-His-Pro-Gly). This sequence was replace by that which codes for the signal peptide HPLSP of 16 amino acids (ATG CTG CCA CTT TGG ACT CTT TCA CTG CTG CTG GGA GCA GTA GCA GGA)
(SEQ ID NO: 29) fused to that which codes for the first 8 codons of the mature HGL protein ("HPLSP-first 8 codons of mature HGL"). The sequence "HPLSP-first 8 codons of mature HGL" was amplified by PCR from the matrix 5' aaactgcaggctcgagaacaATG CTG CCA CTT TGG ACT CTT TCA CTG CTG CTG GGA GCA GTA GCA
GGA TTG TTT GGA AAA TTA CAT CCT GGA tcc CCT G 3' (SEQ ID NO: 30) using the 2 oligodeoxynucleotides, 5' aaactgcaggctcgagaacaATG C 3' (SEQ ID NO: 31) and 5' C AGG gga TCC AGG ATG TAA TTT TCC 3' (SEQ ID NO: 32), following the PCR amplification protocol described previously (see paragraph I above). The hybridization temperature was adjusted. After double enzymatic digestion by PstI and BamHI, the DNA fragments originating from the PCR amplification were purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al. 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 minutes,

centrifuged at 12000 g for 30 minutes, washed with 70% ethanol, dried, then ligated with plasmid DNA of pBIOC84 double digested by PstI and BamHI, purified by electrophoresis over 0.8% agarose gel, electroeluted (Sambrook et al., 1989), subjected to precipitation with alcohol, dried. Ligation was carried out with 100 ng of vector and 50 ng of digested DNA fragments originating from the PCR amplification described above, in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli Dh5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml ampicillin, was extracted by the alkaline lysis method (Birnboim and Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. Certain retained clones were verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The sequences of HPLSP and mature HGL were cloned while maintaining their open reading frames (that is to say, such that they constitute a unique open reading frame). The restriction sequence between the sequences HPLSP and mature HGL is Gly-Leu. The resulting plasmid was called pBIOC86.

Detailed Description Text - DETX (184):

The plasmid pBIOC84 was double digested by PstI and BamHI in order to suppress the sequence which codes for the signal peptide HGLSP and the first 8 amino acids of the mature HGL protein (Leu-Phe-Gly-Lys-Leu-His-Pro-Gly). This sequence was replace by that which codes for the signal peptide RGLSP of 19 amino acids (ATG TGG GTG CTT TTC ATG GTG GCA GCT TTG CTA TCT GCA CTT GGA ACT
ACA CAT GGT) (SEQ ID NO: 33) fused to that which codes for the first 8 codons of the mature HGL protein ("RGLSP-first 8 codons of mature HGL"). The sequence "RGLSP-first 8 codons of mature HGL" was amplified by PCR from the matrix 5' aaactgcaggctcgagaacaATG CTG CCA CTT TGG ACT CTT TCA CTG CTG CTG GGA GCA GTA GCA
GGA TTG TTT GGA AAA TTA CAT CCT GGA tcc CCT G 3' (SEQ ID NO: 34) using the 2 oligodeoxynucleotides, 5' aaactgcaggctcgagaacaATG TGG 3' (SEQ ID NO: 35) and 5' C AGG gga TCC AGG ATG TAA TTT TCC 3' (SEQ ID NO: 32), following the PCR amplification protocol described previously (see paragraph I above). The hybridization temperature was adjusted. After double enzymatic digestion by PstI and BamHI, the DNA fragments originating from the PCR amplification were purified by electrophoresis over 2% agarose gel, electroeluted (Sambrook et al. 1989), precipitated in the presence of 1/10 volume of 3M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for minutes, centrifuged at 12000 g for 30 minutes, washed with 70% ethanol, dried, then ligated with plasmid DNA of pBIOC84 double digested by PstI and BamHI, purified by electrophoresis over 0.8% agarose gel, electoeluted (Sambrook et al., 1989), subjected to precipitation with alcohol, dried. Ligation was carried out with 100 ng of vector and 50 ng of digested DNA fragments originating from the PCR amplification described above, in a reaction medium of 10 .mu.l in the presence of 1 .mu.l of the buffer T4 DNA ligase.times.10 (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. The bacteria Escherichia coli Dh5.alpha., rendered competent beforehand, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml ampicillin, was extracted by the alkaline lysis method (Birnboim and

Doly, 1979) and analysed by enzymatic digestion by restriction enzymes. Certain retained clones were verified by sequencing with the aid of the T7.TM. sequencing kit, marketed by Pharmacia, by the dideoxynucleotide method (Sanger et al., 1977). The sequences of RGLSP and mature HGL were cloned while maintaining their open reading frames (that is to say, such that they constitute a unique open reading frame). The restriction sequence between the sequences RGLSP and mature HGL is Gly-Leu. The resulting plasmid was called pBIOC88.

Detailed Description Text - DETX (291):

1 gram of lyophilized leaves is ground at 4.degree. C. in 30 ml of 20 mM glycine buffer, pH 2.5, and the mixture is stirred gently for 15 minutes. During the steeping, the pH is kept at 2.5 by addition of iN HCl. The product of the steeping is centrifuged at 15,000 g for 5 minutes. The pH of the supernatant is adjusted to 4 by addition of 1N NaOH. After filtration over MIRACLOTH (Calbiochem), all the supernatant is applied to a cation exchange resin column (S-Sepharose Fast Flow resin--Pharmacia) of 10 ml (diameter 1.6 cm) equilibrated in a buffer of 20 mM sodium **acetate,** pH 4.0, and 20 mM NaCl at a flow rate of 1 ml per minute. Fractions of 2 ml are collected. After passage of the supernatant, the column is washed with 40 ml of the equilibration buffer. The proteins retained on the column are eluted in accordance with the following protocol: linear gradient in mM sodium **acetate** buffer, pH 4.0, of 20 mM to 210 mM NaCl in the course of 30 minutes for elution of a first set of peaks of proteins which do not contain lipase activity, the test being carried out on analytical samples of 1 ml, plateau at 210 mM NaCl for 20 minutes, linear gradient in 20 mM sodium **acetate** buffer, pH 4.0, of 210 mM to 500 mM NaCl in the course of 30 minutes for elution of a second set of peaks. The lipase activity-measured on analytical samples of 0.5 ml is eluted during this second gradient at an ionic strength of between 300 and 400 mM.

Detailed Description Text - DETX (305):

2 grams of lyophilized leaves is ground up at 4.degree. C. in 60 ml of 0.2 M NaCl, pH 3, and the mixture is gently agitated for 15 minutes at 4.degree. C. During this steeping, the pH is kept at 3 by the addition of 1N HCl. The product of the steeping (homogenate) is centrifuged at 10,000 g for 10 minutes. After filtration over MIRACLOTH (Calbiochem) and a 0.45.mu. MILLIPORE filter, all the supernatant is injected into a cation exchange resin column (RESOURCE S 6 ml--Pharmacia--16 mm i.d..times.30 mm) equilibrated in a buffer of 20 mM sodium **acetate,** 0.2 M NaCl pH 3 at a flow rate of 8 ml/minute (240 cm h-1).

Detailed Description Text - DETX (306):

After passage of the non-retained fraction, the column is washed with 30 times its volume of the equilibration buffer. The proteins retained on the column are eluted with a linear gradient in 20 mM sodium **acetate** buffer, pH 3, of 0.2 M NaCl to 0.5 M NaCl in 7 column volumes. Fractions of 4 ml are collected.

Detailed Description Text - DETX (320):

The seed extract is dialyzed against a buffer of 10 mM of sodium **acetate,**

pH4, 140 mM of NaCl, 3 mM of KCl then applied to an immunoaffinity column constituted by dog gastric anti-lipase polyclonal antibodies obtained from guinea-pigs coupled to a resin (hydrazide Avidgel--BIOPROBE INTERNATIONAL, Inc.).

Detailed Description Text - DETX (321):

The resin/seed extract contact is for 30 minutes at 4.degree. C. under gentle agitation. The resin is then rinsed with 10 column volumes of buffer, 10 mM sodium **acetate,** pH4, 150 mM NaCl, 3 mM KCl. The DGL is eluted with 5 column volumes of buffer, 0.2 M glycine, pH 2.8, 150 mM NaCl. The collected fractions have a volume equal to 1 column volume and contain 1/20th V/V of 1M Tris buffer, pH 9. Analysis by electrophoresis over polyacrylamide gel in denaturing medium shows a protein of molecular weight of about 37 kDa.

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DOCUMENT-IDENTIFIER: US 6489100 B1

TITLE: Microorganisms and methods for overproduction of DAHP by cloned **PPS gene**

DATE-ISSUED: December 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Liao; James C.	Los Angeles	CA	N/A	N/A

APPL-NO: 09/ 440503

DATE FILED: November 15, 1999

PARENT-CASE:

This is a request for filing a Continuation under 37 C.F.R. .sctn.1.60 of prior Ser. No. 08/801,454 filed on Feb. 18, 1997, now U.S. Pat. No. 5,906,925, and of prior Ser. No. 09/277,183 filed on Mar. 26, 1999, to be issued as U.S. Pat. No. 5,985,617, both of JAMES C. LIAO for MICROORGANISMS AND METHODS FOR OVERPRODUCTION OF DAHP BY CLONED **PPS GENE**.

US-CL-CURRENT: 435/6, 435/105 , 435/108 , 435/200 , 435/72 , 536/23.2 , 536/23.7 , 536/24.1

ABSTRACT:

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The overexpression of phosphoenol pyruvate synthase increases DAHP production to near theoretical yields.

10 Claims, 14 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

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Abstract Text - ABTX (1):
Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom.

The overexpression of phosphoenol pyruvate synthase increases DAHP production to near theoretical yields.

TITLE - TI (1):
Microorganisms and methods for overproduction of DAHP by cloned **PPS gene**

Parent Case Text - PCTX (1):
This is a request for filing a Continuation under 37 C.F.R. .sctn.1.60 of prior Ser. No. 08/801,454 filed on Feb. 18, 1997, now U.S. Pat. No. 5,906,925, and of prior Ser. No. 09/277,183 filed on Mar. 26, 1999, to be issued as U.S. Pat. No. 5,985,617, both of JAMES C. LIAO for MICROORGANISMS AND METHODS FOR OVERPRODUCTION OF DAHP BY CLONED **PPS GENE**.

Brief Summary Text - BSTX (18):
The present invention provides genetically engineered strains of microorganisms that overexpress the **pps gene** for increasing the production of DAHP to near theoretical yields. The present invention also provides genetically engineered strains of microorganisms where at least one of the plasmids pPS341, pPSL706, pPS706, or derivatives thereof is transformed into a microorganism for increasing the production of DAHP to near theoretical yields.

Brief Summary Text - BSTX (19):
The present invention further provides a method for increasing carbon flow for the biosynthesis of DAHP in a host cell comprising the steps of transforming into the host cell recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced levels relative to wild type host cells, concentrating the transformed cells through centrifugation, resuspending the cells in a minimal, nutrient lean medium, fermenting the resuspended cells, and isolating DAHP from the medium.

Brief Summary Text - BSTX (20):
The present invention further provides methods of increasing carbon flow into the common aromatic pathway of a host cell comprising the step of transforming the host cell with recombinant DNA comprising a **pps gene so that Pps** is expressed at appropriate point in the metabolic pathways at enhanced levels relative to wild type host cells.

Brief Summary Text - BSTX (24):
The present invention further provides a genetic element comprising a **pps gene** and one or more genes selected from the group consisting of an aroF gene, aroG gene, aroH gene, and an aroB gene.

Brief Summary Text - BSTX (25):
The present invention further provides a DNA molecule comprising a vector carrying a **gene coding for Pps**.

Detailed Description Text - DETX (3):

The inventor have found that cell lines can be developed that increase the carbon flux into DAHP production and achieve near theoretical yields of DAHP by overexpressing phosphoenolpyruvate synthase (Pps) in the cell lines. Overexpression of Pps can increase the final concentration and yield of DAHP by as much as two-fold, to a near theoretical maximum as compared to wild type cell lines. The overexpression of Pps is achieved by transforming a cell line with recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced level relative to the wild type cell line and so that the yield of DAHP approaches its theoretical value.

Detailed Description Text - DETX (5):

Besides the use of the **pps gene,** the present invention also provides for transfer of genetic elements comprising the tkt gene, the gene coding for DAHP synthase (aroF in E. coli), the gene coding for 3-dehydroquinate synthase (arob in E. coli), or other genes encoding enzymes that catalyze reactions in the common aromatic pathway. Such a cell transformation can be achieved by transferring one or more plasmids that contain genes that code for enzymes that increase the carbon flux for DAHP synthesis and for subsequent synthesis of other desired cyclic, pre-aromatic, and aromatic metabolites. As a result of this transfer of genetic element(s), more carbon enters and moves through the common aromatic pathway relative to wild type host cells not containing the genetic elements of the present invention.

Detailed Description Text - DETX (6):

In one embodiment, the present invention comprises a method for increasing carbon flow into the common aromatic pathway of a host cell by increasing the production of DAHP through the overexpression of Pps at the appropriate point in the common aromatic pathway to provide additional PEP at the point where PEP condenses with E4P. Increasing carbon flow requires the step of transforming the host cell with recombinant DNA containing a **pps gene so that Pps** is overexpressed at enhanced levels relative to wild type host cells. DAHP is then produced by fermentation of the transformed cell in a nutrient medium where the DAHP can be extracted from the medium on a batch wise or continuous extraction procedure.

Detailed Description Text - DETX (7):

In another embodiment, the present invention involves the co-overexpression of a **pps gene** and other genes coding for enzymes of the common aromatic pathway where additional genetic material is transformed into the host cell. The genes transferred can include the tkt gene, DAHP synthase gene and DHQ synthase gene (preferably the aroF or aroB genes, respectively). Although the work so far has centered around transforming certain host cell strains of E. coli such as AB2847 aroB, this particular host cell may not be the preferred host cells for the commercial production of DAHP or DAHP metabolites through the overexpression of Pps.

Detailed Description Text - DETX (8):

Another embodiment of the present invention is a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway. This method involves the step of increasing expression of Pps in the host cell relative to a wild type host cell. The step of increasing expression of Pps can include transferring into the host cell a vector carrying the **pps gene**. The overexpression of Pps results in forcing increased carbon flow into the biosynthesis of DAHP.

Detailed Description Text - DETX (9):

In another embodiment of the present invention, a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway relative to wild type host cell's biosynthetic production of such compound is provided. This method requires the step of increasing expression in a host cell of a protein catalyzing conversion of pyruvate to PEP. The expression of such a protein can involve transferring into the host cell recombinant DNA including a **pps gene**.

Detailed Description Text - DETX (10):

In another preferred embodiment, the present invention comprises a genetic element comprising the **pps gene** and a gene selected from the group consisting of a aroF gene, a aroB gene, and a tkt gene. Such a genetic element can comprise plasmid pPS341, a vector carrying a **pps gene**.

Detailed Description Text - DETX (50):

In previous work, the inventor demonstrated that overexpression of Pps in host cells cultured on nutrient rich, glucose containing medium led to growth inhibition, increased glucose consumption, and excretion of pyruvate and **acetate**. Their previous study also showed that the effects of Pps overexpression on DAHP production, in actively growing cultures, are not as significant, and that the adverse effects of Pps overexpression on cell growth negated any beneficial effects on DAHP production.

Detailed Description Text - DETX (54):

PEP is also a precursor to the pathways that utilize the Ppc enzyme coded by the ppc gene. It has been reported that the deletion of ppc increased the production of phenylalanine and **acetate**. Moreover, it has been shown that the overexpression of Ppc in a wild-type host reduces **acetate** production. Both results may indicate that the flux through Ppc (from PEP to OAA) is reasonably significant under those conditions, and thus, the modulation of Ppc expression level may affect the utilization of PEP. However, in the present invention, deleting the chromosomal ppc gene did not have a positive effect on DAHP production, suggesting that the flux through Ppc is not important in the methods of the present invention.

Detailed Description Text - DETX (55):

One preferred embodiment of the present invention encompasses modification of a host cell to cause overexpression of an enzyme having the catalytic

properties of naturally derived Pps, and, thereby maximizing the yield of DAHP to near theoretical yields. Enzymes having the catalytic activity of Pps include, but are not limited to, Pps produced by expression in whole cells of a naturally derived **pps gene,** enzymes produced by expression in whole cells of a naturally derived **pps gene** modified by sequence deletion or addition so that the expressed enzyme has an amino acid **sequence that varies from unmodified Pps,** abzymes produced to have catalytic sites with steric and electronic properties corresponding to catalytic sites of Pps, or other proteins produced to have the capability of catalyzing the conversion of pyruvate to PEP by any other art recognized means.

Detailed Description Text - DETX (57):

Additionally, the transformation of DNA, including the **pps gene,** into microorganisms engineered for the overexpression of other substrates, and/or overexpression or derepression of enzymes in the pentose phosphate or common aromatic pathway can be used to tailor the microorganism to achieve near theoretical yields of such DAHP metabolites as tyrosine, tryptophan, phenylalanine, and other aromatic metabolites such as indigo, catechol and quinoid organics such as quinic acid, benzoquinone, and hydroquinone.

Detailed Description Text - DETX (72):

Plasmid pPS341 was constructed by cloning a fragment of E. coli chromosomal DNA containing **pps gene** into an IPTG-inducible expression vector pUHE23-2 (a pBR322 derivative) as taught by Patnaik et al., and the contents of which are herein incorporated by reference. Plasmid pPS341X1 containing the inactive **gene product of pps** was constructed by codon insertion mutagenesis, the details of wvlhich are fully described in Patnaik et al. The **pps gene** on pPS341 was inserted with a Mu dII1734 lac.sup.+ Km.sup.r (MudK) according to published protocol of Castiho et al., the contents of which are herein incorporated by reference. Briefly, a Mu lysate was made from a donor strain POII1734/pPS341, which was lysogenized by the mini-Mu element and a Mu cts. The lysate was used to infect a Mu lysogen of HG4 pps pck, and colonies were selected for Ap.sup.r and Km.sup.r simultaneously to ensure that the mini-Mu element hopped to the plasmid. Colonies were further screened for Pps.sup.- phenotype (inability to grow on pyruvate). Restriction analysis of plasmid DNA further confirmed the insertion of the MudK element into the **pps gene** on plasmid pPS341. 20% of these selected colonies showed IPTG-dependent expression of .beta.-galactosidase, indicating an in-frame insertion. Plasmid from one such colony was named pPS1734, which was then linearized at the Scal site, and then transformed into strain JC7623 recB21 recC22 sbcB15. Transformants were selected for Km.sup.r and scored for Ap sensitivity. Such colonies presumably contained pps::MudK on the chromosome. By use of P1 transduction, this locus was moved to AB2847 and Km.sup.r transductants were further screened for inability to grow on pyruvate. One such colony was designated JCL1362 and used for later studies. The MudK insertion into chromosomal pps was further confirmed by cotransduction frequency (89%) with Tet.sup.r marker from strain CAG12151 zdh-925::Tn10.

Detailed Description Text - DETX (75):

The plasmid pPS706 was constructed by inserting a 2.4 kb PCR fragment containing the promoter-less **pps gene** into the vector pJF118EH. The primers were designed from the published **pps sequence** and contained an EcoRI site and a .phi.10 ribosome binding site upstream of the **pps sequence** and a BainzHI site downstream of the sequence. The PCR product was then cloned into the EcoRI and BaZizHI sites of pJF118EH. Positive clones were selected based on complementation of HG4 pps for growth on pyruvate. Expression of pps from this construct is controlled by the tac promoter inducible by IPTG.

Detailed Description Text - DETX (76):

The plasmid pPSL706 was then constructed from pPS706 as shown in FIG. 5. Briefly, a ScaI/EcoRI fragment containing the **pps gene** was cut from pPS706 and purified from the restriction buffer. This fragment was then cloned into a purified ScaI-EcoRI fragment containing the luxI' promoter from pGS103, kindly given to the inventor by Tom Baldwin. Department of Biochemistry and Biophysics, Texas A&M University. Expression using this system is controlled by the autoinducer (AI) in the culture media. pPSL706 is ampicillin resistant and compatible with other pACYC184 derivatives such as pRWS and pATI. The strains and plasmids used are summarized in Table I and Table II.

Detailed Description Text - DETX (88):

To gain insight into the metabolic flux distribution, the culture broth was analyzed for fermentation byproducts by use of HPLC. Samples were taken from cultures in glucose media with varying activities of Pps, AroG, and TktA. Results indicate that the host strain AB2847 produced **acetate,** succinate, and formate as the major byproducts when neither AroG nor Pps was overexpressed. Production of these acids generally decreased with the increase in IPTG concentration, except formate. This decrease correlates with the increase in DAHP production. When AB2847/pAT1/pPS706 was cultured in glucose with IPTG concentration beyond 50 mM, the broth had undetectable levels of these acids (data not shown). While levels of formic and acetic acid decreased with increase in. Pps activity, succinic acid either remained constant (0 .mu.M IPTG) or increased (10.50 .mu.M IPTG) with an increase in Pps activity. This increase could be contributed to Pps induced increase in PEP level, which is spilled over through PEP carboxylase and eventually to succinate.

Detailed Description Text - DETX (91):

This example demonstrates that the E. Coli AB2847 is unable to utilize DAHP, and accumulates DAHP in the medium if DAHP synthase is overexpressed. This strain was used as a host for detecting the flux committed to the aromatic pathways. Since Draths et al. (Draths, K. M., D. L. Pompliano, D. L. Conley, J. W. Frost, A. Berry, G. L. Disbrow, R. J. Staversky, and J. C. Lievense, "Biocatalytic synthesis of aromatics from D-glucose: The role of transketolase," J. Am. Chem. Soc., 1992, 114, 3956-3962) have shown a possible limitation in the production of DAHP by E4P, pATI (containing both aroG.sup.fbr and tktA) was transformed into AB2847 to eliminate the limitation of E4P. To test whether PEP supply limits DAHP production, PEP synthase (Pps) was overexpressed in AB2847/pAT1 by transforming plasmid pPS341 into this strain. 20-70 copies of the **pps gene** were expressed in the host cells. As a control, pPS341 was substituted by pPS341.times.1, which encodes an inactive, but stable

pps gene product. The use of the inactive Pps control allowed discrimination between the effect of Pps activity and that of protein overexpression.

Detailed Description Text - DETX (97):

As shown above, Pps overexpression improved DAHP production from glucose. We were interested to know whether the basal level of Pps expression in glucose medium contributed to the production of DAHP. Therefore, the chromosomal **pps gene** in strain AB2847 was knocked out. The resulting strain (JCL1362) was used as the host to repeat the above experiments. Results show that inactivation of chromosomal pps did not significantly affect the DAHP production in strains containing pRW5 or pAT1 (FIG. 2B). Therefore, the basal level of pps expression in glucose medium did not contribute to the DAHP production.

Detailed Description Text - DETX (102):

To produce tryptophan, strain ATCC31743 which contains chromosomal markers such as trpR .DELTA.(trpAE) tna can be used as a host. This strain also contains a plasmid pSC102trp which harbors trpAE operon. Plasmids pAT1 and pPS341 (or pPS706 or pPSL706) can be transformed into this strain. The serA gene can be cloned into any of the plasmids. Alternatively, these cloned **genes (trpAE, aroG, tktt, pps** or serA) can be consolidated to one or two plasmids. The resulting strain was grown in MT medium which contains, per liter: KH.sub.2 PO.sub.4, 3 g: K.sub.2 HPO.sub.4, 3g; K.sub.2 HPO.sub.4, 7 g; NH.sub.4 CL, 3 g; MgSO.sub.4, 0.2 g; FeSO.sub.4 7H.sub.2 O), 10 mg, glucose, 0 to 30 g.

Detailed Description Text - DETX (116):

Quinoid organics can be derived fromr dehydroquinate which is a down-stream metabolite of DAHP. To produce quinic acid, E. coli AB2848 aroD harboring pTW8090A which contains the gene qad (quinic acid dehydrogenase from Klebsiella pneuinoniae) (ref: Draths, Ward, and Frost, 1992, JACS, 114, 9725-9726), and pKD136 (ref: same as above) which contains tkt, aroF, and aroB genes can be used as a host. The **pps gene** can be cloned into one of these plasmids and be simultaneously overexpressed. It has been reported that at least 80 mM of D-glucose can be converted into 25 mM of quinic acid. After cell removal, quinic acid in the supernatant can be converted into benzoquinone after addition of sulfuric acid and technical grade manganese (IV) dioxide and heating at 100.degree. C. for 1 h. In the absence of acidification, aqueous solutions of purified quinic acid were converted. to hydroquinone in 10% yield upon heating at 100.degree. C. for 18 h with technical grade manganese dioxide.

Claims Text - CLTX (7):

7. A process for the production of DAHP which comprises cultivating a microorganism in a nutrient medium and overexpressing the **Pps gene**.

Claims Text - CLTX (8):

8. The process of claim 7 wherein the step of overexpressing the **Pps gene** comprises transforming a plasmid selected from the group consisting of pPS341, pPSL706, and pPS706 into the microorganism.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2003/06/17 14:01
2	L2	331546	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2003/06/17 14:02
3	L3	76345	promoter$1	USPAT; US-PGPUB	2003/06/17 14:02
4	L4	1383639	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2003/06/17 14:02
5	L5	60	2 near10 4 near10 3	USPAT; US-PGPUB	2003/06/17 14:03
6	L6	9302	pps or phosphoenol adj pyruvate adj synthase$1	USPAT; US-PGPUB	2003/06/17 14:29
7	L7	94	6 near4 (gene$1 or sequence$1)	USPAT; US-PGPUB	2003/06/17 14:29
8	L8	22	7 same (overexpress$ or amplif$10 or increas$8)	USPAT; US-PGPUB	2003/06/17 14:30
9	L9	17	7 and 2	USPAT; US-PGPUB	2003/06/17 14:48
10	L10	6285	lycopene$1 or isoprenoid$1 or carotene$1 or astaxanthin$1	USPAT; US-PGPUB	2003/06/17 14:58
11	L11	1	6 same 10	USPAT; US-PGPUB	2003/06/17 14:58

US-PAT-NO: 6194457

DOCUMENT-IDENTIFIER: US 6194457 B1
See image for Certificate of Correction

TITLE: Liquid eye drop composition

DATE-ISSUED: February 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Braswell; A. Glenn	Marine del Rey	GA	90292	N/A
Absher; Kenneth J.	Carson City	NV	89703	N/A
Duarte; Alex	Nevada City	CA	95959	N/A

APPL-NO: 09/ 015755

DATE FILED: January 29, 1998

PARENT-CASE:

This nonprovisional application claims the benefit of U.S. Provisional Application No. 06/036,516, filed Jan. 29, 1997.

US-CL-CURRENT: 514/547, 514/561 , 514/562 , 514/912

ABSTRACT:

A composition that is used as an eye treatment contains reduced glutathione, vitamin A and vitamin E, as well as one or more of zinc sulfate, boric acid and potassium as buffering agents. The composition also may contain a lubricant and a preservative. The composition is a sterile isotonic solution. The composition is used in a method of treating eyes for the alleviation of irritations and/or dryness, as well as for the prevention and treatment of cataracts.

20 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Brief Summary Text - BSTX (8):

Accordingly, the lens of the eye has an antioxidant defense system to respond to an oxidative stress and maintain the integrity of the lens. Various studies have shown that the antioxidant defense system includes the enzymes glutathione peroxidase, catalase and superoxide dismutase, and the antioxidants vitamin A (ascorbic acid), vitamin E (.alpha.-tocopherol) and .beta.-carotene.

See, for example, Kamei, "Glutathione Levels of the Human Crystalline Lens in Aging", Biol. Pharm. Bull., vol. 16, no. 9, pps. 870-875 (1993); Fletcher et al., "Glutathione and Aging: Ideas and Evidence", The Lancet, vol. 344, pps. 1379-1380 (1994); and Jacques et al., "Antioxidant Status in Persons With and Without Senile Cataracts", Arch. Opthalmol., vol. 106, pps. 337-340 (1988).

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2003/06/17 14:01
2	L2	331546	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2003/06/17 14:02
3	L3	76345	promoter$1	USPAT; US-PGPUB	2003/06/17 14:02
4	L4	1383639	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2003/06/17 14:02
5	L5	60	2 near10 4 near10 3	USPAT; US-PGPUB	2003/06/17 14:03
6	L6	9302	pps or phosphoenol adj pyruvate adj synthase$1	USPAT; US-PGPUB	2003/06/17 14:29
7	L7	94	6 near4 (gene$1 or sequence$1)	USPAT; US-PGPUB	2003/06/17 14:29
8	L8	22	7 same (overexpress$ or amplif$10 or increas$8)	USPAT; US-PGPUB	2003/06/17 14:30
9	L9	17	7 and 2	USPAT; US-PGPUB	2003/06/17 14:48
10	L10	6285	lycopene$1 or isoprenoid$1 or carotene$1 or astaxanthin$1	USPAT; US-PGPUB	2003/06/17 14:58
11	L11	1	6 same 10	USPAT; US-PGPUB	2003/06/17 14:58
12	L12	1563	6 and 2	USPAT; US-PGPUB	2003/06/17 15:01
13	L13	1563	12 and 6	USPAT; US-PGPUB	2003/06/17 15:01
14	L14	3593	10 and 2	USPAT; US-PGPUB	2003/06/17 15:01
15	L15	9	14 and 6	USPAT; US-PGPUB	2003/06/17 15:01

PGPUB-DOCUMENT-NUMBER: 20030036518

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030036518 A1

TITLE: ARTIFICIAL POLYMERIC MEMBRANE STRUCTURE, METHOD FOR PREPARING SAME, METHOD FOR PREPARING THIS POLYMER, PARTICLE AND FILM CONTAINING THIS STRUCTURE

PUBLICATION-DATE: February 20, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
SAMAIN, DANIEL	TOULOUSE		FR	
PEROCHON, ETIENNE	TOULOUSE		FR	

APPL-NO: 09/ 284754

DATE FILED: April 20, 1999

CONTINUED PROSECUTION APPLICATION: This is a publication of a continued prosecution application (CPA) filed under 37 CFR 1.53(d).

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
FR	9613101	1996FR-9613101	October 23, 1996

PCT-DATA:
APPL-NO: PCT/FR97/01891
DATE-FILED: Oct 22, 1997
PUB-NO:
PUB-DATE:
371-DATE:
102(E)-DATE:

US-CL-CURRENT: 514/44, 424/443 , 424/490

ABSTRACT:

The invention concerns an artificial membranous structure analogous to fixed plasmic membranes which comprise a solid substrate (61); a functional membrane (63) which does not circumscribe the external medium; and at least one bifunctional fixing compound (62) inserted between the membrane (63) and the substrate (61), cooperating by polyelectrolytic complexing with the substrate (61) and by lyotropic bonds with the membrane (63). The invention also concerns the use of this structure for obtaining a medicament, a particle, a film, its method of preparation, as well as a lipidic polycationic polymer, and a method for its preparation, acting as a bifunctional compound (62).

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Summary of Invention Paragraph - BSTX (40):
[0040] Advantageously and according to the invention, the membranous ligands are selected from among phospholipids, fatty acids, **isoprenoids,** peptides, fatty amines, ethers, sterols, terpenes, glycolipids, shingolipids, gangliosides and ceramides.

Detail Description Paragraph - DETX (54):
[0152] Preparation of viral particles with a membrane containing DPPE 3-mercaptopropionate. 12 mg of particles containing 10 mg of phospholipids and 200 .mu.g of DPPE (0.26 .mu.mol) were dispersed in 30 ml of a 75 mM sodium **acetate** buffer brought to pH 8.5 by adding a bicarbonate buffer. 100 .mu.l of a 15 mM solution of succinimidyl 3-(-2-pyridyldithio) propionate (SDDP) were added and vigorous stirring was carried out for 1 h. 6 ml of a 1M sodium **acetate** solution were then added. The suspension was then dialysed against a 20 mM sodium **acetate** buffer. 2.3 mg (15 .mu.mol) of dithiothreitol in a sodium carbonate buffer were added and the suspension was kept under argon at pH 7.5 for 1 h. The pH was then adjusted to 5.2 by adding a sodium **acetate** buffer and the suspension was then dialysed against a 20 mM sodium **acetate** buffer. A preparation was obtained containing 0.1 .mu.mol of DPPE modified by mercaptopropionate.

Detail Description Paragraph - DETX (58):
[0156] 1 .mu.mol of modified transferrin dissolved in a 100 mM, pH 7.8, phosphate buffer was mixed with particles containing 0.1 .mu.mol of DPPE 3-mercaptopropionate and dispersed in a 20 mM sodium **acetate** buffer. The preparation was stirred for 24 hours at room temperature and was then subjected to ultrafiltration through a 100 KD membrane to remove excess transferrin.

Detail Description Paragraph - DETX (99):
[0187] The particles were dispersed in 150 ml of a 150 mM **PPS** buffer, of pH 7.1, and gently stirred. Aliquots were withdrawn at regular intervals of time and the concentration of doxorubicin present in the supernatant was measured by/spectrophotometry at 480 nm.

Claims Text - CLTX (7):
7. The membranous structure as claimed in one of claims 1 to 6, wherein the membranous ligands (65, 66) are selected from phospholipids, fatty acids, **isoprenoids** and peptides.

PGPUB-DOCUMENT-NUMBER: 20020094977

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020094977 A1

TITLE: HMG-CoA reductase inhibitors and method

PUBLICATION-DATE: July 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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APPL-NO: 10/ 007407

DATE FILED: December 4, 2001

RELATED-US-APPL-DATA:

child 10007407 A1 20011204

parent continuation-in-part-of 09875155 20010606 US PENDING

non-provisional-of-provisional 60211595 20000615 US

US-CL-CURRENT: 514/215, 514/291 , 540/586 , 546/80

ABSTRACT:

Compounds of the following structure are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids such as lowering LDL cholesterol and/or increasing HDl cholesterol, and treating hyperlipidemia, hypercholesterolemia, hypertriglyceridemia and atherosclerosis 1
and pharmaceutically acceptable salts thereof, wherein X is O, S, SO, SO.sub.2 or NR.sub.7;
Z is 2
n is 0 or 1;
R.sub.1 and R.sub.2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl; and
R.sub.3 to R.sub.10 are as defined herein.

[0001] This application is a continuation-in-part of U.S. application Ser. No. 09/875,155 filed Jun. 6, 2001 which application claims priority from U.S. provisional application No. 60/211,595, filed Jun. 15, 2000.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (195):
[0192] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, .alpha.-phosphono-sulfonates disclosed in U.S. Pat. No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including **isoprenoid** (phosphinylmethyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Pat. No. 4,871,721 and 4,924,024 and in Biller, S. A., Neuenschwander, K., Ponpipom, M. M., and Poulter, C. D., Current Pharmaceutical Design, 2, 1-40 (1996).

Summary of Invention Paragraph - BSTX (210):
[0207] an anti-oxidant such as beta-**carotene,** ascorbic acid, .alpha.-tocopherol or retinol as disclosed in WO 94/15592 as well as Vitamin C and an antihomocysteine agent such as folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E;

Summary of Invention Paragraph - BSTX (290):
[0287] a chondroprotective compound such as a polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (**PPS**), doxycycline or minocycline, such as disclosed in EP 970694;

Detail Description Paragraph - DETX (9):
[0370] A mixture of crude Part B compound (17.0 g, 27.3 mmol), ammonium **acetate** (9.34 g, 120 mmol) and copper **acetate** monohydrate (20.54 g, 101 mmol) in glacial acetic acid (100 ml) was refluxed under argon for 19 hours. The mixture was poured into an ice-cold solution of concentrated ammonium hydroxide (85 ml) in water (170 ml) and the bright blue solution was extracted with ether (3.times.200 ml). The combined organic extracts were washed with water (2.times.80 ml) and brine (80 ml), dried (anhydrous Na.sub.2SO.sub.4), filtered, evaporated to dryness, and dried in vacuo. The crude product (14 g, brown syrup) was chromatographed in two batches, each on a silica gel column (EM, 2-1/4".times.10") to give the desired product as an off-white solid (4.161 g). An additional 931 mg of product was obtained from chromatography of mixed fractions. Yield: 5.092 g, 46% from compound A). Rf 0.53 (Silica gel; EtOAc:Hexane-1:4; UV) 41

Detail Description Paragraph - DETX (10):
[0371] A solution of Part C compound (2.515 g, 6.23 mmol) in dry THF (30 ml) was cooled to 0.degree. C. (ice-water bath), treated dropwise with lithium aluminum hydride (1.0 M in THF; 12.5 ml, 12.5 mmol), stirred at 0.degree. C. for 30 minutes then at room temperature for 3 hours. The reaction mixture was cooled to 0.degree. C., treated successively with water (0.5 ml), 15% NaOH (0.5 ml) and water (1.5 ml), stirred at room temperature for 5 minutes then diluted with ethyl **acetate** (50 ml). The slurry was filtered through a Celite.RTM. pad, washing the pad well with ethyl **acetate** (3.times.25 ml). The clear filtrate was evaporated to dryness and dried in vacuo to give the title

product. Yield: 2.386 g, white foam (100 %). Rf 0.15 (Silica gel; EtOAc:Hexane-1:4; UV) 42

Detail Description Paragraph - DETX (11):

[0372] A solution of Part D compound (2.27 g, 6.23 mmol) in dry dichloromethane (45 ml) was cooled to 0.degree. C. (ice-water bath) and treated dropwise with phosphorus tribromide (1.0 M in dichloromethane; 12.5 ml, 12.5 mmol). The ice bath was removed and the reaction mixture was stirred at room temperature for 30 minutes after which it was re-cooled to 0.degree. C. and treated dropwise with saturated sodium bicarbonate (70 ml). The mixture was then warmed to room temperature and extracted with ethyl **acetate** (2.times.100 ml). The combined organic extracts were washed with water (2.times.50 ml) and brine (50 ml), re-extracting each aqueous wash with dichloromethane (100 ml). The organic extracts were dried (anhydrous sodium sulfate), filtered, evaporated to dryness and dried in vacuo to give the title product as a white solid. Yield: 2.503 g, (94%). m.p.=169-171.degree. C. Rf 0.58 (Silica gel; EtOAc:Hexane- 1:4; UV). 43

Detail Description Paragraph - DETX (12):

[0373] A solution of diethyl phosphite (0.88 ml, 6.83 mmoles) in dry THF (10 ml) was cooled to -10.degree. C. (acetonitrile-dry ice bath), treated with sodium (bistrimethylsilyl)amide (1.0 M in THF; 6.7 ml, 6.7 mmol) and stirred at -10.degree. C. for 30 minutes. The cooled solution was treated with a solution of Part E compound (2.41 g, 5.68 mmol) in dry THF (20 ml), stirred at -10.degree. C. for 1.0 hour then quenched at -10.degree. C. with water (14 ml). The solution was extracted with ethyl **acetate** (2.times.75 ml) and the combined organic extracts washed with 1.0 M hydrochloric acid (8.0 ml) and brine (10 ml), dried (anhydrous sodium sulfate), filtered, evaporated to dryness and dried in vacuo. The crude product (3.12 g, syrup) was chromatographed on a silica gel column (EM, 5.5 cm.times.12.5 cm) to give the title compound as a syrup. Yield: 2.34 g (85.5%). Rf 0.33 (Silica gel; EtOAc-Hexane-1:1; UV). 44

Detail Description Paragraph - DETX (13):

[0374] A solution of Part F compound (2.29 g, 4.756 mmol) in dry THF (20 ml) was cooled to -78.degree. C., treated with 2.37 M n-butyllitium (2.41 ml, 5.71 mmol) and stirred at -78.degree. C. for 40 minutes. The solution was treated dropwise via cannula with a -78.degree. C. solution of Part A(I) compound (2.36 g, 9.15 mmol) in dry THF (10 ml), keeping both solutions at -78.degree. C. at all times. The reaction mixture was stirred at -78.degree. C. for 1.0 hr, -10.degree. C. for 1.0 hr and at room temperature for 5 hr, quenched with 25% ammonium chloride solution (12 ml) then extracted with ethyl **acetate** (2.times.100 ml). The combined organic extracts were washed with 25% ammonium chloride solution (12 ml) and brine (12 ml), dried (anhydrous sodium sulfate), filtered, evaporated to dryness and dried in vacuo. The crude product yellow syrup was chromatographed on a silica gel column (EM, 2-1/4".times.10") to afford the title compound as a syrup. Yield: 878 mg (32%). Rf 0.37 (Silica gel; EtOAc:Hexane-1:4; UV). 45

Detail Description Paragraph - DETX (14):

[0375] A solution of Part G compound (850 mg, 1.45 mmol) in dry dichloromethane (20 ml) was cooled to 0.degree. C., treated with trifluoroacetic acid (1.85 ml, 24 mmol), stirred at 0.degree. C. for 5 minutes, then at room temperature for 4.5 hours. The reaction mixture was poured slowly into a 1 L flask containing ethyl **acetate** (300 ml) and saturated sodium bicarbonate (40 ml), rinsing the flask with ethyl **acetate** (50 ml). The mixture was stirred well and the phases separated, washing the organic phase with saturated sodium bicarbonate (25 ml) and brine (25 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, evaporated to dryness and dried in vacuo. The crude product mixture was chromatographed on a silica gel column (EM, 1.5".times.12") to give the desired compound as a syrup. Yield: 570 mg (83%). Rf 0.23 (Silica gel; EtOAc:Hexane-1:1; UV) 46

Detail Description Paragraph - DETX (64):

[0419] (prepared as described in Example 2 Parts A, B and C except methyl isobutyryl **acetate** is substituted for ethyl isobutyryl **acetate**) and toluene (170 mL). The mixture is stirred at 20-25.degree. C. until a clear solution is obtained. A solutin of 65% Red-Al in toluene (57.8 mL, 192.6 mmol) is added and the reaction mixture is heated to 80.degree. C. until complete as determined by HPLC. The reaction mixture is cooled to 20.degree. C. and quenched by pouring it into cold (0-5.degree. C.) 20% HCl (495 mL). Phases are separated and the spent toluene phase is discarded. The pH of the aqueous phase is adjusted from <0 to 4-5 with 10N NaOH. Ethyl **acetate** (500 mL) is added and the pH adjustment continued to 7-8. The phases are separated. The aqueous phase is extracted with additional ethyl **acetate** (2.times.500 mL). The combined rich ethyl **acetate** solution is washed with water (3.times.250 mL) and concentrated under reduced pressure to .about.465 mL. This solution is carried through to the next oxidation step.

Detail Description Paragraph - DETX (65):

[0420] The rich ethyl **acetate** solution is charged from above into a three neck 1-L flask equipped with mechanical stirring, temperature controller, and addition funnel and cooled to 0-5.degree. C. To the slurry, potassium bromide (1.53 g, 12.8 mmol) and TEMPO (2,2,6,6-tetramethyl-1-piperidinylo- xy) (0.20 g, 1.28 mmol) are added. The pH of NaOCl (sodium hypochlorite) solution (212.1 mL) is adjusted to .about.9.1 and added to the slurry at a rate such that the temperature remained at 0-5.degree. C. Stirring is continued at 0-5.degree. C. until the reaction is complete as determined by HPLC. The aqueous phase is extracted with EtOAc (2.times.200 mL). The combined rich organic phase is washed with a 1:1 solution of sat. aq. Na.sub.2S.sub.2O.sub.3 (sodium thiosulfate) (75 mL) and water (75 mL) followed by wash of the rich organic phase with 1N NaOH (250 mL). The rich organic phase is washed with water (250 mL) and concentrated to .about.100 mL under reduced pressure. Isopropanol (IPA) (400 mL) is added and the resulting mixture is heated to reflux (80-85.degree. C.) . The solution is distilled to a volume of .about.250 mL. Water (50 mL) is added and the crystal slurry is stirred at 70-80.degree. C. for 1 h then allowed to cool to 20-25.degree. C. over at least 1 h. The slurry is held at 20-25.degree. C. for at least 1 h before collecting the solid by filtration on a Buchner funnel. The cake is washed with cold (0.degree. C.) IPA/water (4:1) (2.times.50 mL) and dried to a constant weight under vacuum at

40.degree. C. to afford title aldehyde.

Detail Description Paragraph - DETX (77):

[0428] An N.sub.2 purged 250 mL 3-neck rb flask is charged with Example 27 pyridine derivative (18) (5 g, 13.9 mmol), Example 28 sulfone (16) (6.9 g, 15.3 mmol) and THF (75 mL). The stirred solution is cooled to -74 to -78.degree. C. Slowly a 1M solution of LiHMDS (lithium bis(trimethylsilyl)amide) (15.3 mL, 15.3 mmol) in THF is charged at a rate such that the temperture remained between -70 and -78.degree. C. After addition of the base is complete, the reaciton mixture is warmed to .about.-45.degree. C. over .about.15 minutes. The stirred reaction is quenched at -70.degree. C. by slow addition of sat. aq. NH.sub.4Cl (7.5 mL) solution and water (38 mL). The dry ice bath is removed and the solution is warmed to 20-25.degree. C. from the reaction mixture. Ethyl **acetate** (50 mL) is added, the mixture agitated, and layers separated. The organic layer is washed with saturated sodium bicarbonate solution (2.times.38 mL) followed by brine (25 mL) and concentrated to a volume of 50 mL. Acetonitrile (50 mL) is added and the solution is concentrated to a volume of 50 mL. This step is repeated. Water (.about.5-6 mL) is slowly added to the hot solution (60-70.degree. C.) until the cloud point is reached. The thin slurry is held for 30 min at high temperature and then slowly cooled over several hours with stirring. The product is filtered, cake is washed with a 5:1 mixture of acetonitrile and water, and dried to afford the title compound.

Claims Text - CLTX (41):

40. The combination as defined in claim 21 wherein the other therapeutic agent is an anti-Alzheimer's agent or anti-dementia agent, which is tacrine HCl (Cognex.RTM.), donepezil (Aricept.RTM.), a .gamma.-secretase inhibtor, a .beta.-secretase inhibitor and/or antihypertensive agent; an antiosteoporosis agent, which is parathyroid hormone, a bisphosphonate, alendronate, a Ca receptor agonist or a progestin receptor agonist; a hormone replacement therapeutic agent, which is a selective estrogen receptor modulator (SERM); a tyrosine kinase inhibitor; a selective androgen receptor modulator; an antiarrhythmic agent, which is a .beta.-blocker, or a calcium channel blocker, or an .alpha.-adrenergic blocker; coenzyme Q sub. 10; an agent that upregulates type III endothelial cell nitric acid syntase; a chondroprotective compound which is polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (**PPS**), doxycycline or minocycline; a cyclooxygenase (COX)-2 inhibitor, which is Celebrex.RTM. (Searle) or Vioxx.RTM. (Merck) or a glycoprotein IIa/IIIb receptor antagonist; a 5-HT reuptake inhibitor; a growth hormone secretagogue; an anti-atherosclerosis agent; an anti-infective agent, or an immunosuppressant for use in transplantation, or an antineoplastic agent.

PGPUB-DOCUMENT-NUMBER: 20020061901

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020061901 A1

TITLE: HMG-CoA reductase inhibitors and method

PUBLICATION-DATE: May 23, 2002

INVENTOR-INFORMATION:

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APPL-NO: 10/ 008154

DATE FILED: December 4, 2001

RELATED-US-APPL-DATA:

child 10008154 A1 20011204

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non-provisional-of-provisional 60211594 20000615 US

US-CL-CURRENT: 514/290, 514/278 , 546/15 , 546/79 , 546/93

ABSTRACT:

Compounds of the following structure are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids, for example, lowering LDL cholesterol and/or increasing HDL cholesterol, and treating hyperlipidemia, dyslipidemia, hormone replacement therapy, hypercholesterolemia, hypertriglyceridemia and atherosclerosis as well as Alzheimer's disease and osteoporosis 1
and pharmaceutically acceptable salts thereof, 2
n is 0 or 1;
x is 0, 1, 2, 3 or 4;
y is 0, 1, 2, 3 or 4, provided that at least one of x and y is other than 0;
and optionally one or more carbons of (CH.sub.2).sub.x and/or (CH.sub.2).sub.y together with additional carbons form a 3 to 7 membered spirocyclic ring;
R.sub.1 and R.sub.2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;
R.sub.3 is H or lower alkyl;
R.sub.4 and R.sub.7 are as defined herein.

[0001] This application is a continuation-in-part of U.S. application Ser.

No. 09/875,218 filed Jun. 6, 2001, which application claims priority from U.S. provisional application No. 60/211,594, filed Jun. 15, 2000.

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Summary of Invention Paragraph - BSTX (171):
[0168] Referring to Scheme 5, the arginine salt of the compounds of formula I of the invention may be prepared by treating alkali metal salt (preferably sodium) Ib with acid (TFA, HCl) to form the acid Ib.sup.6 which is treated with arginine in the presence of suitable solvents such as ethyl alcohol and H.sub.2O, ethyl **acetate,** acetonitrile and the like, to form arginine salt Ib.sup.7. 31

Summary of Invention Paragraph - BSTX (192):
[0189] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, .alpha.-phosphono-sulfonates disclosed in U.S. Pat. No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including **isoprenoid** (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Pat. Nos. 4,871,721 and 4,924,024 and in Biller, S. A., Neuenschwander, K., Ponpipom, M. M., and Poulter, C. D., Current Pharmaceutical Design, 2, 1-40 (1996).

Summary of Invention Paragraph - BSTX (207):
[0204] an anti-oxidant such as beta-**carotene,** ascorbic acid, .alpha.-tocopherol or retinol as disclosed in WO 94/15592 as well as Vitamin C and an antihomocysteine agent such as folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E;

Summary of Invention Paragraph - BSTX (287):
[0284] a chondroprotective compound such as a polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (**PPS**), doxycycline or minocycline, such as disclosed in EP 970694;

Detail Description Paragraph - DETX (6):
[0362] To a stirred solution of crude Part C compound (26.9 mmol) in HOAc (128 mL) was added ammonium **acetate** (9.14 g, 118.6 mmol) and copper (II) **acetate** monohydrate (19.7 g, 99.7 mmol). The reaction mixture was heated at reflux under argon overnight. After cooling to room temperature, the reaction mixture was poured into a mixture of NH.sub.4OH (150 mL) and ice (.sup..about.300 g), then extracted with Et.sub.2O (3.times.100 mL). The combined Et.sub.2O extracts were washed with H.sub.2O and brine, then dried (Na.sub.2SO.sub.4), filtered and concentrated in vacuo. Purification by flash chromatography (2:20:80-EtOAc/CH.sub.2Cl.sub.2/hexa- ne) gave the title compound as a white foam, 7.7 g, 71% yield (from Part B compound). 41

Detail Description Paragraph - DETX (17):

[0371] A 1 L 3-necked round bottom flask was flame-dried and then fitted with a mechanical stirrer, an argon-filled balloon, vacuum take-off and a thermocouple. To a stirred slurry of Part (1) compound (7.00 g, 12.9 mmol) in THF (200 mL) at 0.degree. C. was added n-butyllithium solution (5.4 mL, 2.5 M in hexanes, 13.5 mmol) over 20 min. A deep red-orange solution formed. After 30 min, a solution of zinc chloride-N,N,N',N'-tetr- amethylethylene-diamine complex (dried in vacuo at 60.degree. C. for 2 h, 2.42 g, 13.5 mmol) in THF (100 mL) was added via cannula and stirred 30 min. After 30 min, the resulting solution was cannulated into a solution of Example 2 Part G aldehyde (4.30 g, 16.6 mmol) in THF (20 mL) at room temperature over 20 min. A light orange solution soon formed, followed by a precipitate. After 3 h, the reaction was quenched with brine (50 mL) and water (50 mL) and extracted three times with ethyl **acetate** (100 mL). The organic extracts were combined, dried (MgSO.sub.4) and evaporated. LCMS of the crude material indicated unreacted Part (1) compound and an 89/11 mixture of the desired (E) isomer/undesired (Z) isomer.

Detail Description Paragraph - DETX (21):

[0374] To a solution of 4-fluoro-benzaldehyde (5 g, 40.3 mmol) and ethyl isobutyryl **acetate** (6.5 mL, 40.3 mmol) in benzene (50 mL) was added piperidine (400 .mu.l, 4.04 mmol), followed by acetic acid (100 .mu.l, 1.66 mmol). The reaction was refluxed for 16 hours and partitioned between aqueous HCl (1N, 20 mL) and ethyl **acetate** (50 mL .times.2). The combined organic layers were washed with saturated NaHCO.sub.3 (20 mL), brine (10 ml), and dried over sodium sulfate (Na.sub.2SO.sub.4). The solvent was removed in vacuo. Distillation at 140.degree. C. at 300 mm Hg afford 9.06 g (85% yield) of compound A as a yellow oil. ESI-LC/MS (M+H).sup.+=264. 50

Detail Description Paragraph - DETX (23):

[0376] To a solution of the crude compound B (12 g) in aqueous HOAc (100 mL) was added ammonium **acetate** (9.5 g, 123.2 mmol), followed by cupric **acetate** monohydrate (20.7 g, 113.9 mmol). The reaction was reflux for 20 hours, cooled to room temperature, then poured into a solution of ammonium hydroxide in ice (1 to 1; v/v). The aqueous layer was extracted with ethyl ether (200 mL.times.3). The combined organic layers were washed with water (50 mL) and brine (50 mL). Flash chromatography (10% ethyl **acetate** in hexane) afforded 10.2 g (88% yield) of compound C as white powder. ESI-LC/MS (M+H).sup.+=404; m.p. 138-140.degree. C. 52

Detail Description Paragraph - DETX (24):

[0377] To a solution of compound C (10 g, 24.78 mmol) in anhydrous THF (240 mL) at 0.degree. C. was added 1.0 M lithium aluminum hydride in THF (74 mL, 74 mmol). The reaction was stirred at 0.degree. C. for 1 hour and then warmed to room temperature and stirred for 16 hours. The reaction was then cooled to 0.degree. C. and quenched slowly with ice, then sodium hydroxide (10% NaOH, 20 mL). The mixture was extracted with diethyl ether (50 mL.times.2) and filtered. The filter cake was then washed with more ethyl ether (10 mL) and ethyl **acetate** (10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), then dried over sodium sulfate (Na.sub.2SO.sub.4). Flash chromatography (20% ethyl **acetate** in hexane) afforded 6.5 g (73% yield)

of compound D. ESI-LC/MS (M+H).sup.+=362; m.p. 170-171.degree. C. 53

Detail Description Paragraph - DETX (25):

[0378] To a solution of compound D (8.5 g, 23.54 mmol) in anhydrous CH.sub.2Cl.sub.2 (100 mL) at 0.degree. C. was slowly added 1.0 M phosphorous tribromide in CH.sub.2Cl.sub.2 (47 mL, 47.1 mmol) while maintaining the temperature below 10.degree. C. After the addition was complete, the reaction was stirred at 0.degree. C. for 1 hour and then poured into saturated cold NaHCO.sub.3solution (200 mL) with stirring. The aqueous layer was extracted with CH.sub.2Cl.sub.2 (50 ml.times.2) and the combined organic layer was washed with water (10 mL) and brine (10 mL), then dried over sodium sulfate (Na.sub.2SO.sub.4). Flash chromatography (10% ethyl **acetate** in hexane) gave 8.6 g (86% yield) of compound E as a white solid. ESI-LC/MS (M+H).sup.+=424; m.p. 157-159.degree. C. 54

Detail Description Paragraph - DETX (26):

[0379] To a solution of diethyl phosphite (785 .mu.L, 6.09 mmol) in anhydrous THF (25 mL) at -10.degree. C. under argon was added a 1.0 M THF solution of sodium hexamethyldisazide (6 mL, 6.09 mmol). The reaction mixture was stirred at -10.degree. C. for 30 minutes. A solution of compound E (2.15 g, 5.08 mmol) in THF was added to the reaction while maintaining the temperature at -10.degree. C. After the addition was complete, the reaction was stirred for 1 hour and quenched with water (20 mL). The aqueous layer was extracted with ethyl **acetate** (30 mL.times.2) and the combined organic layers were washed with iN HCl solution (5 mL). The organic solvent was removed in vacuo. Flash chromatography using 20% to 30% ethyl **acetate** in hexane as eluting afforded 2.29 g (94% yield) of compound F as a white solid. ESI-LC/MS (M+H).sup.+=482; m.p. 102-105.degree. C. 55

Detail Description Paragraph - DETX (29):

[0382] To a cooled (-78.degree. C.) solution of compound F (2.02 g, 4.19 mmol) in anhydrous THF (30 mL) under argon was slowly added a 2.5 M THF solution of n-butyllithium (2.1 mL) over a period of 40 minutes. The temperature was maintained below -75.degree. C. during the addition. After the addition was complete, the reaction mixture was stirred for another 40 minutes at -78.degree. C. A solution of compound G (2.2 g, 8.52 mmol) in THF under argon was cannulated into the phosphonate mixture at -78.degree. C. After the addition was complete, the reaction was stirred for 1 hour at -78.degree. C. The reaction was then warmed to -10.degree. C. and stirred for 1 hour and then stirred at room temperature for an additional hour. The mixture was quenched with saturated ammonium chloride solution (5 mL) and extracted with ethyl **acetate** (60 mL.times.3). The combined organic layers were washed with water (10 mL) and brine (10 mL), then dried over sodium sulfate (Na.sub.2SO.sub.4) and filtered. The filtrate was concentrated in vacuo. Flash chromatography using 5% to 10% ethyl **acetate** in hexane as eluent afforded 1.48 g (60% yield) of compound H as a white solid. ESI-LC/MS (M+H).sup.+=586; m.p. 148-149.degree. C. 57

Detail Description Paragraph - DETX (30):

[0383] To a cooled (0.degree. C.) solution of compound H (500 mg, 0.854 mmol) in anhydrous CH.sub.2Cl.sub.2 (12 mL) under argon was slowly added trifluroacetic acid (987 mL, 12.82 mmol). After the addition was complete, the reaction mixture was allowed to stirred at 0.degree. C. for 10 minutes and at room temperature for 3 hours and then the solvent was removed in vacuo. The reaction mixture was quenched with phosphate solution (pH 7.5, 12 mL) and extracted with CH.sub.2Cl.sub.2 (20 mL.times.2). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate (Na.sub.2SO.sub.4), and filtered. The solvent was removed in vacuo. Flash silica gel chromatography using 30% to 50% ethyl **acetate** in hexane as an eluent afforded 331 mg (80% yield) of compound I as a white powder. ESI-LC/MS (M+H).sup.+=588; m.p. =199-200.degree. C. 58

Detail Description Paragraph - DETX (38):

[0389] To part H(1) compound (109 mg, 0.2 mmol) in 25 mL 2-necked round bottom flask (flame-dried and fitted with an argon-filled balloon, vacuum take-off and a thermocouple) was added 0.5 mL of DMPU (distilled over CaH.sub.2 under reduced pressure, stored with 4A molecular sieves). The resulting slurry was warmed while stirring until becoming a clear solution, which was diluted with THF (1.5 mL). The reaction mixture was evacuated and purged three times with argon, then cooled to -78.degree. C. To the cooled reaction mixture was added dropwise 0.42 mL of a 0.5 M solution of LDA in THF.sup.1 (0.21 mmol). An amber colored solution formed. After stirring at -78.degree. C. for 30 minutes, a solution of Example 2 Part G aldehyde (67 mg, 0.26 mmol) in THF (0.5 mL) was added via a syringe. After addition, the resulting yellow solution was stirred at -78.degree. C. for 30 minutes, then at 0.degree. C. for 1 hour before quenched with an aqueous solution of ammonium chloride. The reaction mixture was extracted three times with ethyl **acetate** (10 mL). The organic extracts were combined, washed with water and brine, dried (MgSO.sub.4) and evaporated. The crude product was purified using flash chromatography on silica gel eluting with 5% EtOAc/hexane. The desired fractions were pooled and concentrated, and the collected residue dried in vacuo overnight to give Part H(2) compound as a white foam, 80 mg (68% yield).

Detail Description Paragraph - DETX (43):

[0393] To a cooled (0.degree. C.) solution of Part A compound (450 mg, 0.766 mmol) in anhydrous CH.sub.2Cl.sub.2 (9 mL) under argon was slowly added trifluroacetic acid (886 mL, 12.5 mmol). After the addition was complete, the reaction mixture was allowed to stirred at 0.degree. C. for 10 minutes and at room temperature for 3 hours and then the solvent was removed in vacuo. The reaction mixture was quenched with phosphate solution (pH 7.5, 12 mL) and extracted with CH.sub.2Cl.sub.2 (20 mL.times.2). The combined organic layer was washed with brine (saturated NaCl solution, 10 ml), dried over sodium sulfate (Na.sub.2SO.sub.4) and filtered. The solvent was removed in vacuo. Flash silica gel chromatography using 30% to 50% ethyl **acetate** in hexane as an eluent afford 330 mg (91% yield) part B compound as a white powder. ESI-LC/MS (M+H).sup.+=474, MP (.degree. C.)=253-254. 63

Detail Description Paragraph - DETX (54):

[0402] To a mixture of 4-fluoro-benzaldehyde (935.8 g, 7.54 moles) and

methyl isobutyryl **acetate** (1087 g, 7.54 moles) was added piperidine (64.2 g, 0.75 mol), followed by acetic acid (22.6 g, 0.38 mol). The mixture was heated to 80 to 85.degree. C. for about 2 hours. 16 Liters (4.times.4L) of toluene was added and mixed with the reaction mixture. The toluene was removed using a rotavapor (50-65.degree. C./20-90 torr), leaving a yellow oil. The yellow oil was dissolved in 5 L MTBE and washed with:

Detail Description Paragraph - DETX (60):

[0408] To a solution of the crude compound B (3078 g) in aqueous HOAc (16 L) was added ammonium **acetate** (1446 g), followed by cupric **acetate** monohydrate (1859 g). The reaction was refluxed between 120 to 124.degree. C. for 12-15 hours. Approximately 90% of the acetic acid was evaporated to produce a green slurry. The slurry was then mixed with 14 L MTBE.

Detail Description Paragraph - DETX (66):

[0414] To a 500 mL round bottom flask equipped with a magnetic stirrer and a nitrogen inlet was charged Part C compound (17) (Scheme 6) (50.0 g, 128.4 mmol) and toluene (170 mL). The mixture was stirred at 20-25.degree. C. until a clear solution was obtained. A solutin of 65% Red-Al in toluene (57.8 mL, 192.6 mmol) was added and the reaction mixture was heated to 80.degree. C. until complete as determined by HPLC. The reaction mixture was cooled to .about.20.degree. C. and quenched by pouring it into cold (0-5.degree. C.) 20% HCl (495 mL). Phases were separated and the spent toluene phase was discarded. The pH of the aqueous phase was adjusted from <0 to 4-5 with 10N NaOH. Ethyl **acetate** (500 mL) was added and the pH adjustment continued to 7-8. The phases were separated. The aqueous phase was extracted with additional ethyl **acetate** (2.times.500 mL). The combined rich ethyl **acetate** solution was washed with water (3.times.250 mL) and concentrated under reduced pressure to .about.465 mL. This solution was carried through to the next oxidation step.

Detail Description Paragraph - DETX (67):

[0415] The rich ethyl **acetate** solution was charged from above into a three neck 1-L flask equipped with mechanical stirring, temperature controller, and addition funnel and cooled to 0-5.degree. C. To the slurry, potassium bromide (1.53 g, 12.8 mmol) and TEMPO (2,2,6,6-tetramethyl-1-piperidinylo- xy) (0.20 g, 1.28 mmol) were added. The pH of NaOCl (sodium hypochlorite) solution (212.1 mL) was adjusted to 9.1 and added to the slurry at a rate such that the temperature remained at 0-5.degree. C. Stirring was continued at 0-5.degree. C. until the reaction was complete as determined by HPLC. The aqueous phase was extracted with EtOAc (2.times.200 mL). The combined rich organic phase was washed with a 1:1 solution of sat. aq. Na.sub.2S.sub.2O.sub.3 (sodium thiosulfate) (75 mL) and water (75 mL) followed by wash of the rich organic phase with 1N NaOH (250 mL). The rich organic phase was washed with water (250 mL) and concentrated to .about.100 mL under reduced pressure. Isopropanol (IPA) (400 mL) was added and the resulting mixture was heated to reflux (80-85.degree. C.). The solution was distilled to a volume of .about.250 mL. Water (50 mL) was added and the crystal slurry was stirred at 70-80.degree. C. for 1 h then allowed to cool to 20-25.degree. C. over at least 1 h. The slurry was held at 20-25.degree. C. for at least 1 h before collecting the solid by filtration on a Buchner funnel. The cake was washed with cold (0.degree. C.)

IPA/water (4:1) (2.times.50 mL) and dried to a constant weight under vacuum at 40.degree. C. to afford 41.5 g (90%) of title aldehyde as a white crystalline solid.

Detail Description Paragraph - DETX (74):

[0420] A.sub.n N.sub.2 purged 250 mL 3-neck rb flask was charged with Example 35 pyridine derivative (18) (5.0 g, 13.9 mmol), Example 36 sulfone (16) (6.92 g, 15.3 mmol) and THF (75 mL). The stirred solution was cooled to -74 to -78.degree. C. Slowly a 1M solution of LIHMDS (lithium bis(trimethylsilyl)amide) (15.3 mL, 15.3 mmol) in THF was charged at a rate such that the temperature remained between -70 and -78.degree. C. After addition of the base was complete, the reaction mixture was warmed to .about.-45.degree. C. over .about.15 minutes. The stirred reaction was quenched at -70.degree. C by slow addition of sat. aq. NH_4Cl (7.5 mL) solution and water (38 mL). The dry ice bath was removed and the solution was warmed to 20-25.degree. C. from the reaction mixture. Ethyl **acetate** (50 mL) was added, the mixture agitated, and layers separated. The organic layer was washed with saturated sodium bicarbonate solution (2.times.38 mL) followed by brine (25 mL) and concentrated to a volume of 50 mL. Acetonitrile (50 mL) was added and the solution was concentrated to a volume of 50 mL. This step was repeated. Water (.about.5-6 mL) was slowly added to the hot solution (60-70.degree. C.) until the cloud point was reached. The thin slurry was held for 30 min at high temperature and then slowly cooled over several hours with stirring. The product was filtered, cake was washed with a 5:1 mixture of acetonitrile and water, and dried to afford 7.5 g (91%) of the title compound as a white crystalline material.

Detail Description Paragraph - DETX (80):

[0424] was transferred to a 5.0-liter round bottom flask equipped with a mechanical stirrer, a thermometer, and a septa. While temperature was controlled at <29.degree. C., 1 N HCl (aq) was added to the above aqueous layer until the pH=6.94. Subsequently, 330 mL of ethyl **acetate** was added to the aqueous layer followed by charging more 1 N HCl (aq) until pH=2.82. After separating and saving the ethyl **acetate** layer, the aqueous layer was extracted with ethyl **acetate** (330 mL.times.3). The combined ethyl **acetate** layers containing acid Ib.sup.8 of the invention 75

Detail Description Paragraph - DETX (81):

[0425] were washed with 50% brine (265 mL), brine (427 mL), separated and mixed with a suspension of L-arginine (27.4 g, 157 mmol) in ethanol (276 mL) and water (138 mL). The mixture was evaporated to dryness under reduced pressure at ca 45-50.degree. C. To the resulting white solid were added ethyl **acetate** (450 mL), ethanol (316 mL), and water (145 mL) followed by heating the white suspension to 50.degree. C. Another 36.7 mL of water was added to dissolve all solids at 56.degree. C; subsequently 1720 mL of ethy **acetate** was added to the hot solution to initialize the crystallization. The white suspension was stirred at 50.degree. C. for 1.5 h and at ambient for 13 h. After filtration, the crystalline solid was washed with 143 mL of a mixture of EtOAc (200 mL), EtOH (12 mL) and H_2O (6 mL) and was dried in vacuo at 40-50.degree. C. for 24 h. The title product obtained as a white solid weighed

78.9 (g). Yield, 75.7%. [.alpha.].sup.25.sub.D=+23.0 (c 0.31, CH.sub.3CN:H.sub.2O, 1:1, v/v).

Claims Text - CLTX (37):

36. The combination as defined in claim 17 wherein the other therapeutic agent is an anti-Alzheimer's agent or anti-dementia agent, which is tacrine HCl (Cognex.RTM.), donepezil (Aricept.RTM.), a .gamma.-secretase inhibtor, a .beta.-secretase inhibitor and/or antihypertensive agent; an antiosteoporosis agent, which is parathyroid hormone, a bisphosphonate, alendronate, a Ca receptor agonist or a progestin receptor agonist; a hormone replacement therapeutic agent, which is a selective estrogen receptor modulator (SERM); a tyrosine kinase inhibitor; a selective androgen receptor modulator; an antiarrhythmic agent, which is a .beta.-blocker, or a calcium channel blocker, or an .alpha.-adrenergic blocker; coenzyme Q sub. 10; an agent that upregulates type III endothelial cell nitric acid syntase; a chondroprotective compound which is polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (**PPS**), doxycycline or minocycline; a cyclooxygenase (COX)-2 inhibitor, which is Celebrex.RTM. (Searle) or Vioxx.RTM. (Merck) or a glycoprotein IIa/IIIb receptor antagonist; a 5-HT reuptake inhibitor; a growth hormone secretagogue; an anti-atherosclerosis agent; an anti-infective agent, or an immunosuppressant for use in transplantation, or an antineoplastic agent.

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ABSTRACT:

Compounds of the following structure are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids, for example, lowering LDL cholesterol and/or increasing HDL cholesterol, and treating hyperlipidemia, dyslipidemia, hormone replacement therapy, hypercholesterolemia, hypertriglyceridemia and atherosclerosis as well as Alzheimer's disease and osteoporosis 1
and pharmaceutically acceptable salts thereof, 2
n is 0 or 1;
x is 0, 1, 2, 3 or 4;
y is 0, 1, 2, 3 or 4, provided that at least one of x and y is other than 0;
and optionally one or more carbons of (CH.sub.2), and/or (CH.sub.2).sub.y together with additional carbons form a 3 to 7 membered spirocyclic ring;
R.sub.1 and R.sub.2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl;
R.sub.3 is H or lower alkyl;
R.sub.4 and R.sub.7 are as defined herein.

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Summary of Invention Paragraph - BSTX (168):

[0164] Referring to Scheme 5, the arginine salt of the compounds of formula I of the invention may be prepared by treating alkali metal salt (preferably sodium) Ib with acid (TFA, HCl) to form the acid Ib.sup.6 which is treated with arginine in the presence of suitable solvents such as ethyl alcohol and H.sub.2O, ethyl **acetate,** acetonitrile and the like, to form arginine salt Ib.sup.7. 25

Summary of Invention Paragraph - BSTX (189):

[0185] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, .alpha.-phosphono-sulfonates disclosed in U.S. Pat. No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including **isoprenoid** (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Pat. No. 4,871,721 and 4,924,024 and in Biller, S. A., Neuenschwander, K., Ponpipom, M. M., and Poulter, C. D., Current Pharmaceutical Design, 2, 1-40 (1996).

Summary of Invention Paragraph - BSTX (204):

[0200] an anti-oxidant such as beta-**carotene,** ascorbic acid, .alpha.-tocopherol or retinol as disclosed in WO 94/15592 as well as Vitamin C and an antihomocysteine agent such as folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E;

Summary of Invention Paragraph - BSTX (284):

[0280] a chondroprotective compound such as a polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (**PPS**), doxycycline or minocycline, such as disclosed in EP 970694;

Summary of Invention Paragraph - BSTX (361):

[0357] To a stirred solution of crude Part C compound (26.9 mmol) in HOAc (128 mL) was added ammonium **acetate** (9.14 g, 118.6 mmol) and copper (II) **acetate** monohydrate (19.7 g, 99.7 mmol). The reaction mixture was heated at reflux under argon overnight. After cooling to room temperature, the reaction mixture was poured into a mixture of NH.sub.4OH (150 mL) and ice (.about.300 g), then extracted with Et.sub.2O (3.times.100 mL). The combined Et.sub.2O extracts were washed with H.sub.2O and brine, then dried (Na.sub.2SO.sub.4), filtered and concentrated in vacuo. Purification by flash chromatography (2:20:80-EtOAc/CH.sub.2Cl.sub.2/hexa- ne) gave the title compound as a white foam, 7.7 g, 71% yield (from Part B compound). 35

Detail Description Paragraph - DETX (4):

[0366] A 1 L 3-necked round bottom flask was flame-dried and then fitted with a mechanical stirrer, an argon-filled balloon, vacuum take-off and a thermocouple. To a stirred slurry of Part (1) compound (7.00 g, 12.9 mmol) in THF (200 mL) at 0.degree. C. was added n-butyllithium solution (5.4 mL, 2.5 M in hexanes, 13.5 mmol) over 20 min. A deep red-orange solution formed. After 30 min, a solution of zinc chloride-N,N,N1,N'-tetr- amethylethylene-diamine complex (dried in vacuo at 60.degree. C. for 2h, 3.42 g, 13.5 mmol) in THF

(100 mL) was added via cannula and stirred 30 min. After 30 min, the resulting solution was cannulated into a solution of Example 2 Part G aldehyde (4.30 g, 16.6 mmol) in THF (20 mL) at room temperature over 20 min. A light orange solution soon formed, followed by a precipitate. After 3 h, the reaction was quenched with brine (50 mL) and water (50 mL) and extracted three times with ethyl **acetate** (100 mL). The organic extracts were combined, dried (MgSO.sub.4) and evaporated. LCMS of the crude material indicated unreacted Part (1) compound and an 89/11 mixture of the desired (E) isomer/undesired (Z) isomer.

Detail Description Paragraph - DETX (8):

[0369] To a solution of 4-fluoro-benzaldehyde (5 g, 40.3 mmol) and ethyl isobutyryl **acetate** (6.5 mL, 40.3 mmol) in benzene (50 mL) was added piperidine (400 .mu.l, 4.04 mmol), followed by acetic acid (100 .mu.l, 1.66 mmol). The reaction was refluxed for 16 hours and partitioned between aqueous HCl (1N, 20 mL) and ethyl **acetate** (50 mL .times.2). The combined organic layers were washed with saturated NaHCO.sub.3 (20 mL), brine (10 ml), and dried over sodium sulfate (Na.sub.2SO.sub.4). The solvent was removed in vacuo. Distillation at 140.degree. C. at 300 mm Hg afford 9.06 g (85w yield) of compound A as a yellow oil. ESI-LC/MS (M+H).sup.+=264. 44

Detail Description Paragraph - DETX (10):

[0371] To a solution of the crude compound B (12 g) in aqueous HOAc (100 mL) was added ammonium **acetate** (9.5 g, 123.2 mmol), followed by cupric **acetate** monohydrate (20.7g, 113.9 mmol). The reaction was reflux for 20 hours, cooled to room temperature, then poured into a solution of ammonium hydroxide in ice (1 to 1; v/v). The aqueous layer was extracted with ethyl ether (200 mL.times.3). The combined organic layers were washed with water (50 mL) and brine (50 mL). Flash chromatography (10% ethyl **acetate** in hexane) afforded 10.2 g (88% yield) of compound C as white powder. ESI-LC/MS (M+H).sup.+=404; m.p. 138-140.degree. C. 46

Detail Description Paragraph - DETX (11):

[0372] To a solution of compound C (10 g, 24.78 mmol) in anhydrous THF (240 mL) at 0.degree. C. was added 1.0 M lithium aluminum hydride in THF (74 mL, 74 mmol). The reaction was stirred at 0.degree. C. for 1 hour and then warmed to room temperature and stirred for 16 hours. The reaction was then cooled to 0.degree. C. and quenched slowly with ice, then sodium hydroxide (10% NaOH, 20 mL). The mixture was extracted with diethyl ether (50 mL.times.2) and filtered. The filter cake was then washed with more ethyl ether (10 mL) and ethyl **acetate** (10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), then dried over sodium sulfate (Na.sub.2SO.sub.4). Flash chromatography (20% ethyl **acetate** in hexane) afforded 6.5 g (73% yield) of compound D. ESI-LC/MS (M+H).sup.+=362; m.p. 170-171.degree. C. 47

Detail Description Paragraph - DETX (12):

[0373] To a solution of compound D (8.5 g, 23.54 mmol) in anhydrous CH.sub.2Cl.sub.2 (100 mL) at 0.degree. C. was slowly added 1.0 M phosphorous tribromide in CH.sub.2Cl.sub.2 (47 mL, 47.1 mmol) while maintaining the temperature below 10.degree. C. After the addition was complete, the reaction

was stirred at 0.degree. C. for 1 hour and then poured into saturated cold NaHCO.sub.3 solution (200 mL) with stirring. The aqueous layer was extracted with CH.sub.2Cl.sub.2 (50ml.times.2) and the combined organic layer was washed with water (10 mL) and brine (10 mL), then dried over sodium sulfate (Na.sub.2SO.sub.4). Flash chromatography (10% ethyl **acetate** in hexane) gave 8.6 g (86% yield) of compound E as a white solid. ESI-LC/MS (M+H).sup.+=424; m.p. 157-159.degree. C. 48

Detail Description Paragraph - DETX (13):

[0374] To a solution of diethyl phosphite (785 .mu.L, 6.09 mmol) in anhydrous THF (25 mL) at -10.degree. C. under argon was added a 1.0 M THF solution of sodium hexamethyldisazide (6 mL, 6.09 mmol). The reaction mixture was stirred at -10.degree. C. for 30 minutes. A solution of compound E (2.15 g, 5.08 mmol) in THF was added to the reaction while maintaining the temperature at -10.degree. C. After the addition was complete, the reaction was stirred for 1 hour and quenched with water (20 mL). The aqueous layer was extracted with ethyl **acetate** (30 mL.times.2) and the combined organic layers were washed with iN HCl solution (5 mL). The organic solvent was removed in vacuo. Flash chromatography using 20% to 30% ethyl **acetate** in hexane as eluting afforded 2.29 g (94% yield) of compound F as a white solid. ESI-LC/MS (M+H).sup.+=482; m.p. 102-105.degree. C. 49

Detail Description Paragraph - DETX (16):

[0377] To a cooled (-78.degree. C.) solution of compound F (2.02 g, 4.19 mmol) in anhydrous THF (30 mL) under argon was slowly added a 2.5 M THF solution of n-butyllithium (2.1 mL) over a period of 40 minutes. The temperature was maintained below -75.degree. C. during the addition. After the addition was complete, the reaction mixture was stirred for another 40 minutes at -78.degree. C. A solution of compound G (2.2 g, 8.52 mmol) in THF under argon was cannulated into the phosphonate mixture at -78.degree. C. After the addition was complete, the reaction was stirred for 1 hour at -78.degree. C. The reaction was then warmed to -10.degree. C. and stirred for 1 hour and then stirred at room temperature for an additional hour. The mixture was quenched with saturated ammonium chloride solution (5 mL) and extracted with ethyl **acetate** (60 mL.times.3). The combined organic layers were washed with water (10 mL) and brine (10 mL), then dried over sodium sulfate (Na.sub.2SO.sub.4) and filtered. The filtrate was concentrated in vacuo. Flash chromatography using 5% to 10% ethyl **acetate** in hexane as eluent afforded 1.48 g (60% yield) of compound H as a white solid. ESI-LC/MS (M+H).sup.+=586; m.p. 148-149.degree. C. 51

Detail Description Paragraph - DETX (17):

[0378] To a cooled (0.degree. C.) solution of compound H (500 mg, 0.854 mmol) in anhydrous CH.sub.2Cl.sub.2 (12 mL) under argon was slowly added trifluroacetic acid (987 mL, 12.82 mmol). After the addition was complete, the reaction mixture was allowed to stirred at 0.degree. C. for 10 minutes and at room temperature for 3 hours and then the solvent was removed in vacuo. The reaction mixture was quenched with phosphate solution (pH 7.5, 12 mL) and extracted with CH.sub.2Cl.sub.2 (20 mL.times.2). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate (Na.sub.2SO.sub.4),

and filtered. The solvent was removed in vacuo. Flash silica gel chromatography using 30% to 50% ethyl **acetate** in hexane as an eluent afforded 331mg (80% yield) of compound I as a white powder. ESI-LC/MS (M+H).sup.+=588; m.p.=199-200.degree. C. 52

Detail Description Paragraph - DETX (25):

[0385] To part H(I) compound (109 mg, 0.2 mmol) in 25 mL 2-necked round bottom flask (flame-dried and fitted with an argon-filled balloon, vacuum take-off and a thermocouple) was added 0.5 mL of DMPU (distilled over CaH.sub.2 under reduced pressure, stored with 4A molecular sieves). The resulting slurry was warmed while stirring until becoming a clear solution, which was diluted with THF (1.5 mL). The reaction mixture was evacuated and purged three times with argon, then cooled to -78.degree. C. To the cooled reaction mixture was added dropwise 0.42 mL of a 0.5 M solution of LDA in THF.sup.1 (0.21 mmol). An amber colored solution formed. After stirring at -78.degree. C. for 30 minutes, a solution of Example 2 Part G aldehyde (67 mg, 0.26 mmol) in THF (0.5 mL) was added via a syringe. After addition, the resulting yellow solution was stirred at -78.degree. C. for 30 minutes, then at 0.degree. C. for 1 hour before quenched with an aqueous solution of ammonium chloride. The reaction mixture was extracted three times with ethyl **acetate** (10 mL). The organic extracts were combined, washed with water and brine, dried (MgSO.sub.4) and evaporated. The crude product was purified using flash chromatography on silica gel eluting with 5% EtOAc/hexane. The desired fractions were pooled and concentrated, and the collected residue dried in vacuo overnight to give Part H(2) compound as a white foam, 80 mg (68% yield).

Detail Description Paragraph - DETX (30):

[0389] To a cooled (0.degree. C.) solution of Part A compound (450mg, 0.766 mmol) in anhydrous CH.sub.2Cl.sub.2 (9 mL) under argon was slowly added trifluroacetic acid (886 mL, 12.5 mmol). After the addition was complete, the reaction mixture was allowed to stirred at 0.degree. C. for 10 minutes and at room temperature for 3 hours and then the solvent was removed in vacuo. The reaction mixture was quenched with phosphate solution (pH 7.51 12 mL) and extracted with CH.sub.2Cl.sub.2 (20 mL.times.2) . The combined organic layer was washed with brine (saturated NaCl solution, 10 ml), dried over sodium sulfate (Na.sub.2SO.sub.4) and filtered. The solvent was removed in vacuo. Flash silica gel chromatography using 30% to 50% ethyl **acetate** in hexane as an eluent afford 330mg (91% yield) part B compound as a white powder. ESI-LC/MS (M+H).sup.+=474, MP (.degree. C.)=253-254. 57

Detail Description Paragraph - DETX (44):

[0400] To a mixture of 4-fluoro-benzaldehyde (935.8 g, 7.54 moles) and methyl isobutyryl **acetate** (1087 g, 7.54 moles) was added piperidine (64.2 g, 0.75 mol), followed by acetic acid (22.6 g, 0.38 mol). The mixture was heated to 80 to 85.degree. C. for about 2 hours. 16 Liters (4.times.4 L) of toluene was added and mixed with the reaction mixture. The toluene was removed using a rotavapor (50-65.degree. C./20-90 torr), leaving a yellow oil. The yellow oil was dissolved in 5 L MTBE and washed with:

Detail Description Paragraph - DETX (50):

[0406] To a solution of the crude compound B (3078 g) in aqueous HOAc (16 L) was added ammonium **acetate** (1446 g), followed by cupric **acetate** monohydrate (1859 g). The reaction was refluxed between 120 to 124.degree. C. for 12-15 hours. Approximately 90% of the acetic acid was evaporated to produce a green slurry. The slurry was then mixed with 14 L MTBE.

Detail Description Paragraph - DETX (56):

[0412] To a 500 mL round bottom flask equipped with a magnetic stirrer and a nitrogen inlet was charged Part C compound (17) (Scheme 6) (50.0 g, 128.4 mmol) and toluene (170 mL) . The mixture was stirred at 20-25.degree. C. until a clear solution was obtained. A solutin of 65% Red-Al in toluene (57.8 mL, 192.6 mmol) was added and the reaction mixture was heated to 80.degree. C. until complete as determined by HPLC. The reaction mixture was cooled to -20.degree. C. and quenched by pouring it into cold (0-5.degree. C.) 20% HCl (495 mL) . Phases were separated and the spent toluene phase was discarded. The pH of the aqueous phase was adjusted from <0 to 4-5 with 1ON NaOH. Ethyl **acetate** (500 mL) was added and the pH adjustment continued to 7-8. The phases were separated. The aqueous phase was extracted with additional ethyl **acetate** (2.times.500 mL). The combined rich ethyl **acetate** solution was washed with water (3.times.250 mL) and concentrated under reduced pressure to -465 mL. This solution was carried through to the next oxidation step.

Detail Description Paragraph - DETX (57):

[0413] The rich ethyl **acetate** solution was charged from above into a three neck 1-L flask equipped with mechanical stirring, temperature controller, and addition funnel and cooled to 0-5.degree. C. To the slurry, potassium bromide (1.53 g, 12.8 mmol) and TEMPO (2,2,6,6-tetramethyl-1-piperidinylo- xy) (0.20 g, 1.28 mmol) were added. The pH of NaOCl (sodium hypochlorite) solution (212.1 mL) was adjusted to -9.1 and added to the slurry at a rate such that the temperature remained at 0-5.degree. C. Stirring was continued at 0-5.degree. C. until the reaction was complete as determined by HPLC. The aqueous phase was extracted with EtOAc (2.times.200 mL). The combined rich organic phase was washed with a 1:1 solution of sat. aq. Na.sub.2S.sub.2O.sub.3 (sodium thiosulfate) (75 mL) and water (75 mL) followed by wash of the rich organic phase with 1N NaOH (250 mL). The rich organic phase was washed with water (250 mL) and concentrated to -100 mL under reduced pressure. Isopropanol (IPA) (400 mL) was added and the resulting mixture was heated to reflux (80-85.degree. C.). The solution was distilled to a volume of -250 mL. Water (50 mL) was added and the crystal slurry was stirred at 70-80.degree. C. for 1 h then allowed to cool to 20-25.degree. C. over at least 1 h. The slurry was held at 20-25.degree. C. for at least 1 h before collecting the solid by filtration on a Buchner funnel. The cake was washed with cold (0.degree. C.) IPA/water (4:1) (2.times.50 mL) and dried to a constant weight under vacuum at 40.degree. C. to afford 41.5 g (90%) of title aldehyde as a white crystalline solid.

Detail Description Paragraph - DETX (64):

[0418] An N.sub.2 purged 250 mL 3-neck rb flask was charged with Example 35 pyridine derivative (18) (5.0 g, 13.9 mmol), Example 36 sulfone (16) (6.92 g, 15.3 mmol) and THF (75 mL). The stirred solution was cooled to -74 to

-78.degree. C. Slowly a 1M solution of LIHMDS (lithium bis(trimethylsilyl)amide) (15.3 mL, 15.3 mmol) in THF was charged at a rate such that the temperture remained between -70 and -78.degree. C. After addition of the base was complete, the reaciton mixture was warmed to -45.degree. C. over -15 minutes. The stirred reaction was quenched at -70.degree. C by slow addition of sat. aq. NH.sub.4Cl (7.5 mL) solution and water (38 mL). The dry ice bath was removed and the solution was warmed to 20-25.degree. C. from the reaction mixture. Ethyl **acetate** (50 mL) was added, the mixture agitated, and layers separated. The organic layer was washed with saturated sodium bicarbonate solution (2.times.38 mL) followed by brine (25 mL) and concentrated to a volume of 50 mL. Acetonitrile (50 mL) was added and the solution was concentrated to a volume of 50 mL. This step was repeated. Water (.about.5-6 mL) was slowly added to the hot solution (60-70.degree. C.) until the cloud point was reached. The thin slurry was held for 30 min at high temperature and then slowly cooled over several hours with stirring. The product was filtered, cake was washed with a 5:1 mixture of acetonitrile and water, and dried to afford 7.5 g (91%) of the title compound as a white crystalline material.

Detail Description Paragraph - DETX (69):

[0422] was transferred to a 5.0-liter round bottom flask equipped with a mechanical stirrer, a thermometer, and a septa. While temperature was controlled at <29.degree. C., 1 N HCl (aq) was added to the above aqueous layer until the pH=6.94. Subsequently, 330 mL of ethyl **acetate** was added to the aqueous layer followed by charging more 1 N HCl (aq) until pH=2.82. After separating and saving the ethyl **acetate** layer, the aqueous layer was extracted with

Detail Description Paragraph - DETX (70):

[0423] ethyl **acetate** (330 mL.times.3). The combined ethyl **acetate** layers containing acid Ib.sup.8 of the invention 70

Detail Description Paragraph - DETX (71):

[0424] were washed with 50% brine (265 mL), brine (427 mL), separated and mixed with a suspension of L-arginine (27.4 g, 157 mmol) in ethanol (276 mL) and water (138 mL). The mixture was evaporated to dryness under reduced pressure at ca 45-50.degree. C. To the resulting white solid were added ethyl **acetate** (450 mL), ethanol (316 mL), and water (145 mL) followed by heating the white suspension to 50.degree. C. Another 36.7 mL of water was added to dissolve all solids at 56.degree. C.; subsequently 1720 mL of ethy **acetate** was added to the hot solution to initialize the crystallization. The white suspension was stirred at 50.degree. C. for 1.5 h and at ambient for 13 h. After filtration, the crystalline solid was washed with 143 mL of a mixture of EtOAc (200 mL), EtOH (12 mL) and H.sub.2O (6 mL) and was dried in vacuo at 40-50.degree. C. for 24 h. The title product obtained as a white solid weighed 78.9 (g). Yield, 75.7%. [.alpha.].sup.25D=+23.0 (c 0.31, CH.sub.3CN:H.sub.2O, 1:1, v/v).

Claims Text - CLTX (37):

36. The combination as defined in claim 17 wherein the other therapeutic agent is an anti-Alzheimer's agent or anti-dementia agent, which is tacrine HCl (Cognex.RTM.), donepezil (Aricept.RTM.), a .gamma.-secretase inhibtor, a .beta.-secretase inhibitor and/or antihypertensive agent; an antiosteoporosis agent, which is parathyroid hormone, a bisphosphonate, alendronate, a Ca receptor agonist or a progestin receptor agonist; a hormone replacement therapeutic agent, which is a selective estrogen receptor modulator (SERM); a tyrosine kinase inhibitor; a selective androgen receptor modulator; an antiarrhythmic agent, which is a .beta.-blocker, or a calcium channel blocker, or an .alpha.-adrenergic blocker; coenzyme Q sub. 10; an agent that upregulates type III endothelial cell nitric acid syntase; a chondroprotective compound which is polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (**PPS**), doxycycline or minocycline; a cyclooxygenase (COX)-2 inhibitor, which is Celebrex.RTM. (Searle) or Vioxx.RTM. (Merck) or a glycoprotein IIa/IIIb receptor antagonist; a 5-HT reuptake inhibitor; a growth hormone secretagogue; an anti-atherosclerosis agent; an anti-infective agent, or an immunosuppressant for use in transplantation, or an antineoplastic agent.

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ABSTRACT:

Compounds of the following structure are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids such as lowering LDL cholesterol and/or increasing HDl cholesterol, and treating hyperlipidemia, hypercholesterolemia, hypertriglyceridemia and atherosclerosis 1
and pharmaceutically acceptable salts thereof, wherein X is O or S; 2
n is 0 or 1;
R.sub.1 and R.sub.2 are the same or different and are independently selected from alkyl, arylalkyl, cycloalkyl, alkenyl, cycloalkenyl, aryl, heteroaryl or cycloheteroalkyl; and
R.sub.3 to R.sub.9 are as defined herein.

[0001] This application claims priority from U.S. provisional application No. 60/211,595, filed Jun. 15, 2000.

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Detail Description Paragraph - DETX (78):

[0178] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, a-phosphono-sulfonates disclosed in U.S. Pat. No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No.

10, pp 1869-1871, including **isoprenoid** (phosphinyl-methyl)phosphonate- s as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Pat. No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

Detail Description Paragraph - DETX (93):

[0193] an anti-oxidant such as beta-**carotene**, ascorbic acid, .alpha.-tocopherol or retinol as disclosed in WO 94/15592 as well as Vitamin C and an antihomocysteine agent such as folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E;

Detail Description Paragraph - DETX (173):

[0273] a chondroprotective compound such as a polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (**PPS**), doxycycline or minocycline, such as disclosed in EP 970694;

Detail Description Paragraph - DETX (254):

[0353] A mixture of crude Part B compound (17.0 g, 27.3 mmol), ammonium **acetate** (9.34 g, 120 mmol) and copper **acetate** monohydrate (20.54 g, 101 mmol) in glacial acetic acid (100 ml) was refluxed under argon for 19 hours. The mixture was poured into an ice-cold solution of concentrated ammonium hydroxide (85 ml) in water (170 ml) and the bright blue solution was extracted with ether (3.times.200 ml). The combined organic extracts were washed with water (2.times.80 ml) and brine (80 ml), dried (anhydrous Na.sub.2SO.sub.4), filtered, evaporated to dryness, and dried in vacuo. The crude product (14 g, brown syrup) was chromatographed in two batches, each on a silica gel column (EM, 2-1/4".times.10") to give the desired product as an off-white solid (4.161 g). An additional 931 mg of product was obtained from chromatography of mixed fractions. Yield: 5.092 g, 46% from compound A). Rf 0.53 (Silica gel; EtOAc:Hexane-1:4; UV) 36

Detail Description Paragraph - DETX (255):

[0354] A solution of Part C compound (2.515 g, 6.23 mmol) in dry THF (30 ml) was cooled to 0.degree. C. (ice-water bath), treated dropwise with lithium aluminum hydride (1.0 M in THF; 12.5 ml, 12.5 mmol), stirred at 0.degree. C. for 30 minutes then at room temperature for 3 hours. The reaction mixture was cooled to 0.degree. C. treated successively with water (0.5 ml), 15% NaOH (0.5 ml) and water (1.5 ml), stirred at room temperature for 5 minutes then diluted with ethyl **acetate** (50 ml). The slurry was filtered through a Celite.RTM. pad, washing the pad well with ethyl **acetate** (3.times.25 ml). The clear filtrate was evaporated to dryness and dried in vacuo to give the title product. Yield: 2.386 g, white foam (100%). Rf 0.15 (Silica gel; EtOAc:Hexane-1:4; UV). 37

Detail Description Paragraph - DETX (256):

[0355] A solution of Part D compound (2.27 g, 6.23 mmol) in dry dichloromethane (45 ml) was cooled to 0.degree. C. (ice-water bath) and

treated dropwise with phosphorus tribromide (1.0 M in dichloromethane; 12.5 ml, 12.5 mmol). The ice bath was removed and the reaction mixture was stirred at room temperature for 30 minutes after which it was re-cooled to 0.degree. C. and treated dropwise with saturated sodium bicarbonate (70 ml). The mixture was then warmed to room temperature and extracted with ethyl **acetate** (2.times.100 ml). The combined organic extracts were washed with water (2.times.50 ml) and brine (50 ml), re-extracting each aqueous wash with dichloromethane (100 ml). The organic extracts were dried (anhydrous sodium sulfate), filtered, evaporated to dryness and dried in vacuo to give the title product as a white solid. Yield: 2.503 g, (94%). m.p.=169-171.degree. C. Rf 0.58 (Silica gel; EtOAc:Hexane-1:4; UV). 38

Detail Description Paragraph - DETX (257):

[0356] A solution of diethyl phosphite (0.88 ml, 6.83 mmoles) in dry THF (10 ml) was cooled to -10.degree. C. (acetonitrile-dry ice bath), treated with sodium (bistrimethylsilyl)amide (1.0 M in THF; 6.7 ml, 6.7 mmol) and stirred at -10.degree. C. for 30 minutes. The cooled solution was treated with a solution of Part E compound (2.41 g, 5.68 mmol) in dry THF (20 ml), stirred at -10.degree. C. for 1.0 hour then quenched at -10.degree. C. with water (14 ml). The solution was extracted with ethyl **acetate** (2.times.75 ml) and the combined organic extracts washed with 1.0 M hydrochloric acid (8.0 ml) and brine (10 ml), dried (anhydrous sodium sulfate), filtered, evaporated to dryness and dried in vacuo. The crude product (3.12 g, syrup) was chromatographed on a silica gel column (EM, 5.5 cm.times.12.5 cm) to give the title compound as a syrup. Yield: 2.34 g (85.5%). Rf 0.33 (Silica gel; EtOAc-Hexane-1:1; UV). 39

Detail Description Paragraph - DETX (258):

[0357] A solution of Part F compound (2.29 g, 4.756 mmol) in dry THF (20 ml) was cooled to -78.degree. C., treated with 2.37 M n-butyllitium (2.41 ml, 5.71 mmol) and stirred at -78.degree. C. for 40 minutes. The solution was treated dropwise via cannula with a -78.degree. C. solution of Part A(1) compound (2.36 g, 9.15 mmol) in dry THF (10 ml), keeping both solutions at -78.degree. C. at all times. The reaction mixture was stirred at -78.degree. C. for 1.0 hr, -10.degree. C. for 1.0 hr and at room temperature for 5 hr, quenched with 25% ammonium chloride solution (12 ml) then extracted with ethyl **acetate** (2.times.100 ml). The combined organic extracts were washed with 25% ammonium chloride solution (12 ml) and brine (12 ml), dried (anhydrous sodium sulfate), filtered, evaporated to dryness and dried in vacuo. The crude product yellow syrup was chromatographed on a silica gel column (EM, 2-1/4".times.10") to afford the title compound as a syrup. Yield: 878 mg (32%). Rf 0.37 (Silica gel; EtOAc:Hexane-1:4; UV). 40

Detail Description Paragraph - DETX (259):

[0358] A solution of Part G compound (850 mg, 1.45 mmol) in dry dichloromethane (20 ml) was cooled to 0.degree. C., treated with trifluoroacetic acid (1.85 ml, 24 mmol), stirred at 0.degree. C. for 5 minutes, then at room temperature for 4.5 hours. The reaction mixture was poured slowly into a 1 L flask containing ethyl **acetate** (300 ml) and saturated sodium bicarbonate (40 ml), rinsing the flask with ethyl **acetate** (50 ml). The

mixture was stirred well and the phases separated, washing the organic phase with saturated sodium bicarbonate (25 ml) and brine (25 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, evaporated to dryness and dried in vacuo. The crude product mixture was chromatographed on a silica gel column (EM, 1.5".times.12") to give the desired compound as a syrup. Yield: 570 mg (83%). Rf 0.23 (Silica gel; EtOAc:Hexane-1:1; UV) 41

Detail Description Paragraph - DETX (305):

[0401] (50 g, 128.4 mmol) (prepared as described in Example 2 Parts A, B and C except methyl isobutyryl **acetate** is substituted for ethyl isobutyryl **acetate**) and toluene (170 mL). The mixture is stirred at 20-25.degree. C. until a clear solution is obtained. A solutin of 65% Red-Al in toluene (57.8 mL, 192.6 mmol) is added and the reaction mixture is heated to 80.degree. C. until complete as determined by HPLC. The reaction mixture is cooled to .about.20.degree. C. and quenched by pouring it into cold (0-5.degree. C.) 20% HCl (495 mL). Phases are separated and the spent toluene phase is discarded. The pH of the aqueous phase is adjusted from <0 to 4-5 with 10N NaOH. Ethyl **acetate** (500 mL) is added and the pH adjustment continued to 7-8. The phases are separated. The aqueous phase is extracted with additional ethyl **acetate** (2.times.500 mL). The combined rich ethyl **acetate** solution is washed with water (3.times.250 mL) and concentrated under reduced pressure to .about.465 mL. This solution is carried through to the next oxidation step.

Detail Description Paragraph - DETX (306):

[0402] The rich ethyl **acetate** solution is charged from above into a three neck 1-L flask equipped with mechanical stirring, temperature controller, and addition funnel and cooled to 0-5.degree. C. To the slurry, potassium bromide (1.53 g, 12.8 mmol) and TEMPO (2,2,6,6-tetramethyl-l-piperidinylo- xy) (0.20 g, 1.28 mmol) are added. The pH of NaOCl (sodium hypochlorite) solution (212.1 mL) is adjusted to .about.9.1 and added to the slurry at a rate such that the temperature remained at 0-5.degree. C. Stirring is continued at 0-5.degree. C. until the reaction is complete as determined by HPLC. The aqueous phase is extracted with EtOAc (2.times.200 mL). The combined rich organic phase is washed with a 1:1 solution of sat. aq. Na.sub.2S.sub.2O.sub.3 (sodium thiosulfate) (75 mL) and water (75 mL) followed by wash of the rich organic phase with 1N NaOH (250 mL). The rich organic phase is washed with water (250 mL) and concentrated to .about.100 mL under reduced pressure. Isopropanol (IPA) (400 mL) is added and the resulting mixture is heated to reflux (80-85.degree. C.). The solution is distilled to a volume of .about.250 mL. Water (50 mL) is added and the crystal slurry is stirred at 70-80.degree. C. for 1 h then allowed to cool to 20-25.degree. C. over at least 1 h. The slurry is held at 20-25.degree. C. for at least 1 h before collecting the solid by filtration on a Buchner funnel. The cake is washed with cold (0.degree. C.) IPA/water (4:1) (2.times.50 mL) and dried to a constant weight under vacuum at 40.degree. C. to afford title aldehyde.

Detail Description Paragraph - DETX (316):

[0410] A.sub.n N.sub.2 purged 250 mL 3-neck rb flask is charged with Example 27 pyridine derivative (18) (5 g, 13.9 mmol), Example 28 sulfone (16) (6.9 g, 15.3 mmol) and THF (75 mL). The stirred solution is cooled to -74 to

-78.degree. C. Slowly a 1M solution of LiHMDS (lithium bis(trimethylsilyl)amide) (15.3 mL, 15.3 mmol) in THF is charged at a rate such that the temperture remained between -70 and -78.degree. C. After addition of the base is complete, the reaciton mixture is warmed to .about.-45.degree. C. over .about.15 minutes. The stirred reaction is quenched at -70.degree. C. by slow addition of sat. aq. NH.sub.4Cl (7.5 mL) solution and water (38 mL). The dry ice bath is removed and the solution is warmed to 20-25.degree. C. from the reaction mixture. Ethyl **acetate** (50 mL) is added, the mixture agitated, and layers separated. The organic layer is washed with saturated sodium bicarbonate solution (2.times.38 mL) followed by brine (25 mL) and concentrated to a volume of 50 mL. Acetonitrile (50 mL) is added and the solution is concentrated to a volume of 50 mL. This step is repeated. Water (.about.5-6 mL) is slowly added to the hot solution (60-70.degree. C.) until the cloud point is reached. The thin slurry is held for 30 min at high temperature and then slowly cooled over several hours with stirring. The product is filtered, cake is washed with a 5:1 mixture of acetonitrile and water, and dried to afford the title compound.

Claims Text - CLTX (37):

36. The combination as defined in claim 17 wherein the other therapeutic agent is an anti-Alzheimer's agent or anti-dementia agent, which is tacrine HCl (Cognex.RTM.), donepezil (Aricept.RTM.), a .gamma.-secretase inhibtor, a .beta.-secretase inhibitor and/or antihypertensive agent; an antiosteoporosis agent, which is parathyroid hormone, a bisphosphonate, alendronate, a Ca receptor agonist or a progestin receptor agonist; a hormone replacement therapeutic agent, which is a selective estrogen receptor modulator (SERM); a tyrosine kinase inhibitor; a selective androgen receptor modulator; an antiarrhythmic agent, which is a .beta.-blocker, or a calcium channel blocker, or an .alpha.-adrenergic blocker; coenzyme Q sub. 10; an agent that upregulates type III endothelial cell nitric acid syntase; a chondroprotective compound which is polysulfated glycosaminoglycan (PSGAG), glucosamine, chondroitin sulfate (CS), hyaluronic acid (HA), pentosan polysulfate (**PPS**), doxycycline or minocycline; a cyclooxygenase (COX)-2 inhibitor, which is Celebrex.RTM. (Searle) or Vioxx.RTM. (Merck) or a glycoprotein IIa/IIIb receptor antagonist; a 5-HT reuptake inhibitor; a growth hormone secretagogue; an anti-atherosclerosis agent; an anti-infective agent, or an immunosuppressant for use in transplantation, or an antineoplastic agent.

US-PAT-NO: 6572882

DOCUMENT-IDENTIFIER: US 6572882 B1

TITLE: Compositions based on resveratrol

DATE-ISSUED: June 3, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vercauteren; Joseph	Pessac	N/A	N/A	FR
Castagnino; Chantal	Merignac	N/A	N/A	FR
Delaunay; Jean-Claude	Merignac	N/A	N/A	FR

APPL-NO: 09/ 462778

DATE FILED: January 19, 2000

PARENT-CASE:

The present application is a 371 PCT/FR 98/01548, filed Jul. 15, 1998.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	97 08964	July 15, 1997

PCT-DATA:
APPL-NO: PCT/FR98/01548
DATE-FILED: July 15, 1998
PUB-NO: WO99/03816
PUB-DATE: Jan 28, 1999
371-DATE:
102(E)-DATE:

US-CL-CURRENT: 424/451, 424/489 , 514/733 , 514/734

ABSTRACT:

The invention relates to compositions based on derivatives of resveratrol having in particular a high stability as regards air and light.

15 Claims, 5 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

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Brief Summary Text - BSTX (41):

The process for obtaining monomers and oligomers of resveratrol, which is also envisaged by the invention, comprises the following stages extraction by addition, to the vine stalks, of water and/or of organic solvent(s), by subjecting the whole to a treatment such as maceration/lixiviation, ultrasonics or microwaves, delipidation before or after the extraction stage using a solvent of petroleum ether, hexane or chloroform type, additional extraction of the extract recovered by an organic solvent of ethyl **acetate** or ethyl ether type, concentration of the crude extract obtained, and, if desired, its lyophilization.

Brief Summary Text - BSTX (46):

High-performance results have been obtained with a hexane/ethyl **acetate**/ethanol/water mixture with for example the respective proportions of 6/48/11/42 or 4/5/3/3.

Brief Summary Text - BSTX (49):

Similarly, carbonylated or carboxylated solvents can be used instead of ethyl **acetate,** such as acetone, methylethylketone, methylisobutylketone, methylterbutylketone.

Brief Summary Text - BSTX (59):

These medicaments can also contain other active ingredients, in particular products with a protective effect vis-a-vis oxidation reactions. For example .beta.**-carotene** or vitamin E can be mentioned.

Detailed Description Text - DETX (6):

For example, the following are used: water; water/acetone 3/2 or 1/1; methanol; ethanol; water/ethanol: 1/1; water/ethyl **acetate**: 1/1; ethanol/acetone: 1/1; water/ethanol/acetone: 2/1/1, 1/2/1 or 1/1/2

Detailed Description Text - DETX (10):

This extract is in turn subjected to at least one other extraction stage. Ethyl **acetate** or ethyl ether is used at a rate of 3 to 5 times 100 ml.

Detailed Description Text - DETX (13):

FIG. 1 shows the HPLC chromatograph of an ethyl **acetate** extract obtained, after ultrasonic treatment for 2 hours, from 100 g of ground stalks (Merlot type) in 800 ml of water/acetone: 3/2, and delipidation with petroleum ether. Elution was carried out with A: H.sub.2 O/TFA; 100/0.0025 (TFA=trifluoroacetic acid) and B: MeOH/TFA 100/0.0025, according to the gradient

Detailed Description Text - DETX (19):

The extract obtained is then subjected to an extraction stage using ethyl **acetate** or ethyl ether as indicated previously for the preparation of extracts

using ultrasonics or microwaves.

Detailed Description Text - DETX (26):
Main Characteristics of the Device Rotational speed: 0-2000 rpm Column capacity: 230 ml Maximum pressure: 60.times.10.sup.5 Pa. Rotor material: polyphenylenesulphide (**PPS**) Partition disk: series of disks Partition cell: 2136 Cell length: 15 mm.

Detailed Description Text - DETX (27):
The stationary and mobile phases are respectively the lower and upper phases recovered after agitation and decantation of the hexane/ethyl **acetate**/ethanol/water mixture: 6/48/11/42, given the implementation of the technique in ascending mode in this example.

Detailed Description Text - DETX (32):
The 120 mg of ORs recovered in Example 2, dissolved in 2 ml of stationary phase, are separated in ascending mode. The stationary phase constitutes the lower phase of the hexane/ethyl **acetate**/ethanol/water mixture 4/5/3/3 and the mobile phase constitutes the upper phase of the same mixture. The rotational speed is 1100 rpm, the flow rate is 2 ml/minute and the pressure is 44.times.10.sup.5 Pa. Under these conditions, the fraction enriched in resveratrol is collected after 150 minutes of elution and the fraction enriched in resveratrol oligomers is collected after 240 minutes.

Detailed Description Text - DETX (106):
Perlaurate of ORs prepared according to Example 11 is mixed with selenium and vitamin E; Perlaurate of ORs: 85 mg (corresponding to 25 mg of ORs), DL-.alpha.-tocopherol **acetate**: 40 mg, Selenium: 50 mg

US-PAT-NO: 6500463

DOCUMENT-IDENTIFIER: US 6500463 B1

TITLE: Encapsulation of sensitive components into a matrix to obtain discrete shelf-stable particles

DATE-ISSUED: December 31, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
van Lengerich; Bernhard H.	Plymouth	MN	N/A	N/A

APPL-NO: 09/ 410017

DATE FILED: October 1, 1999

US-CL-CURRENT: 424/499, 424/409 , 424/410 , 424/439 , 424/488 , 424/500 , 424/501

ABSTRACT:

A solid active, sensitive encapsulant and/or a liquid encapsulant component which contains an active, sensitive encapsulant, is admixed with at least one plasticizable matrix material, a matrix component which is substantially non-plasticizable at temperatures lower than the decomposition temperature of the encapsulant and which increases the rate of release of the encapsulant from the matrix, and a liquid plasticizer to obtain a formable, extrudable, cuttable, mixture or dough. The matrix material is plasticized by the liquid plasticizer and the encapsulation of the active encapsulant, such as a live microorganism or an enzyme, is accomplished at a low temperature and under low shear conditions. The active component is encapsulated and/or embedded in the plasticizable matrix component or material in a continuous process to produce discrete, solid particles. The formable mixture may be obtained without or substantially no cooking or gelatinizing of the matrix ingredients. A solid encapsulant may be dry-blended with the plasticizable matrix material and the substantially non-plasticizable matrix material, followed by plasticization of the plasticizable matrix material.

92 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Brief Summary Text - BSTX (58):

Additional ingredients which may be used to control the release properties of the final product may be a hydrophobic agent for slowing down the rate of

release of the encapsulant. Exemplary of components which may be added to affect the hydrophobicity of the matrix include fats, oils, waxes, fatty acids, emulsifiers, such as mono- or di- glycerides, synthetic polymers such as polyolefins such as polyethylene or polypropylene, polyvinyl chloride, polyvinyl **acetate** and derivatives thereof, paraffin, and modified starches from plant sources that possess hydrophobic properties that are obtained via either physical or chemical modification, and mixtures of hydrophobic components. Plant lipids or synthetic lipids with melting points up to about 65.degree. C. may, for example, be employed as a hydrophobic agent. The hydrophobic components increase the hydrophobicity of the matrix and help to prevent or delay penetration of water or gastric juice into the matrix by repelling water or aqueous acids, thereby delaying the release of the encapsulant into the surrounding media.

Brief Summary Text - BSTX (67):

Exemplary of the active components which may be encapsulated or embedded in accordance with the present invention are: acepromazine, acetaminophen, acetohexamide, acetohydroxamic acid, acetylcholine, acetylcysteine acyclovir, albendazole, alclometasone dipropionate , allopurinol, alprazolam, alprostadil, amcinoide, amantadine, amdinocillin, amikacin amiloride, aminocaproic acid, aminophylline, aminosalicylate, aminosalicylic acid, amitriptyline hydrochloride, ammonium chloride, amobarbital, amodiaquine hydrochloride, amoxapine, amoxicillin, amphetamine sulfate, amphotericin, ampicillin amprolium, acetazolamide acetyldigoxin, acetylsalicylic acid, anileridine, anthralin, antipyrine, antivenin, apomorphine, apraclonidine, ascorbic acid, aspirin, acromycin atropine, amoxycillin anipamil, azaperone azatadine maleate, azathioprine, azithromycin, aztreonam, bacampicillin, bacitracin, baclofen, barium salts, beclomethasone diproionate, belladonna extract, bendroflumethiazide, benoxinate hydrochloride, benzethonium chloride, benzocaine, benzonatate benzthiazide, benztropine mesylate, betaine, betamethasone, betaxolol, betanechol chloride, biotin, biperiden, bisacodyl, bismuth, botulism antitoxin, bromocriptine mesylate, bromodiphenhydramine hydrochloride, bumetanide, bupivacaine, busulfan butabarbital sodium,butalbital, combinations of butalbital, caffeine and aspirin and codeine, beta**-carotene,** calcifediol, calcium carbonate, calcium citrate, calcium salts, candicidin, captopril, carbachol, carbamazepine, carbenicillin indanyl sodium, carbidopa, carbinoxamine maleate, carboprost tromethamine, carboxymethyl cellulose, carisoprodol, casanthranol, cascara, castor oil, cefaclor, cefadroxil, cefamandole nafate, cefazolin, cefixime, cefoperazone, cefotaxime, cefprozil, ceftazidime, cefuroxime axetil, cephalexin, cephradine, chlorambucil, chloramphenicol, chlordiazepoxide, chloroquine phosphate, chlormadinone **acetate,** chlorothiazide, chlorpheniramine maleate, chloroxylenol, chlorpromazin, chlorpropamide, chlorprothixene, chlorprothixene, chlortetracycline bisulfate, chlortetracycline hydrochloride, chlorthalidone, chlorzoxazone, cholecalciferol, cholera vaccine, chromic chloride, chymotrypsin, cimetidine, cinoxazin, cinoxate, ciprofloxacin, cisplatin, clarithromycin, clavulanate potassium, clemastine fumarate, clidinium bromide, clindamycin hydrochloride, -palmitate and -phosphate, clioquinol, clofazimine, clofibrate, clomiphene citrate, clonazepam, cinnarizine, clonidine hydrochloride, clorsulon, clotrimazole, cloxacillin sodium, cyanocobalamin, cocaine, coccidioidin, cod liver oil, codeine, colchicine, colestipol, corticotropin, corisone **acetate,** cyclacillin, cyclizine hydrochloride,

cyclobenzaprine hydrochloride, cyclophosphamide, cycloserine, cyclosporine, cyproheptadine hydrochloride, cysteine hydrochloride, danazol, dapsone, dehydrocholic acid, demeclocycline, desipramine, desoximetasone, desoxycorticosterone **acetate,** dexamethasone, dexchlorpheniramine maleate, dexpanthenol, dextroamphetamine, dextromethorphan, diazepam, diazoxide, dibucaine, dichlorphenamide, dicloxacillin sodium, dicyclomine, dienestrol, diethylpropion hydrochlorid, diethylstilbestrol, diflunisal, digitalis, dicoumarol, digitoxin, digoxin, dihydroergotamine, dihydrostreptomycin, dihydrotachysterol, dihydroxyaluminium amino **acetate,** dihydroxyaluminium sodium carbonate, diltiazem hydrochloride, dimenhydrinate, dimercaprol, diphenhydramine hydrochloride, diphenoxylate hydrochloride, diphteria antitoxin, dipyridamole, disopyramide phosphate, disulfiram, dobutamine hydrochloride, docusate calcium, docusate sodium, dopamine hydrochloride, doxepin hydrochloride, doxycycline, doxycycline hyclate, doxylamine cuccinate, dronabinol, droperidol, drotaverine, dydrogesterone, dyphylline, guaifenesin, enalapril maleate, analaprilat, ephedrine, epinephrine, equilin, ergocalciferol, ergoloid mesylates, ergonovine maleate, ergotamine tartrate, erythrityl tetranitrate, erythromycin, estradiol, estriol, estrogene, estrone, estropipate, ethcrynic acid, ethambutol hydrochloride, ethchlorvynol, ethinyl estradiol, ethionamide, ethopropazine hydrochloride, ethotoin, ethynodiol diacetate, etidronate disodium, etoposide, eugenol, famotidine, fenoprofen, ferrous fumatate, ferrous gluconate, ferrous sulfate, flucytosine, fludrocortisone **acetate,** flunisolide, fluocinolone acetonide, fluocinonide, fluorescein sodium, fluorometolone, fluorouracil, fluoxymesterone, fluphenazine, flurandrenolide, flurazpam, flurbiprofen, folic acid, furazolidone, flunitrazepam, furosemide, gemfibrozil, gentamicin, gentian violet, glutarate, glutethimide, glycopyrrolate, chorionic gonadotropin, gramicidin, griseofulvin, guaifenesin, guanabenz, guanadrelsulfate, halazone, haloperidol, haloprogin, halothane, heparin calcium, hepatitis virus vaccine, hetacillin potassium, hexylresorcinol, histamine phosphate, histidine, homatropine, histoplasmin, hydralazine hydrochloride, hydrochlorothiazide, hydrocodone bitartrate, hydrocortisone, hexobarbital, hydroflumethiazide, hydromorphone hydrochloride, hydroquinone, hydroxocobalamin, hydroxyamphetamine, hydroxychloroquine sulfate, hydroxyprogesterone caproate, hydroxyurea, hydroxine hydrochloride, hydroxine pamoate, hyoscyamine, hyoscyamine sulfate, ibuprofen, ifosfamide, imipramide, imipramide hydrochloride, indapamide, indomethacin, insulin, inulin, iocetamid, iodoquinol, iohexol, iopamidol, ipecac, ipodate calcium, ipodate sodium, isocarboxacid, isoetharine hydrochloride, isoflurane,isoniacid, isopropamide iodine, isoproterenol hydrochloride, isosorbide dinitrate, isotretenoin, isoxsuprine hydrochloride, kanamycin sulfate, ketoprofen, ketoconazole, labetalol hydrochloride, lanolin, leucine, leucovorin calcium, levamisole hydrochloride, levocamithine, levodopa, levonorgestrel, levorphanol tartrate, levothyroxine sodium, lidocaine, lincomycin hydrochloride, lindane, liothyronine sodium, liotrix, lisinopril, lithium carbonate, loperamide hydrochloride, loracarbef, lonetil, lorazepam, lovastatin, loxapine, lysine, mafenide **acetate,** magaldrte, magnesium carbonate, magnesiumchloride, magnesium gluconate, magnesium oxide, other magnesium salts, malathinon, manganese salts, manganese, maprotiline hydrochloride, mazindol, measle virus vaccine, mebendazole, mebrofenin, mecamylamine hydrochloride, meclizine hydrochloride, meclocycline , meclofenamate sodium, medroxyprogesterone **acetate,** mefenamic acid, megestrol **acetate,** meglumine, melphalan, menadiol sodium diphosphate, menadione, menotropine, meperidine, mephenytoin, mephobarbital, meprednisone,

meprobamate, mercaptopurine, mesoridazine besylate, mestranol, metaproterenol sulfate, metaraminol bitartrate, methacycline hydrochloride, methadone hydrochloride, methamphetamine hydrochloride, methazolamide, methdilazine, methenamine, methicillin sodium, methimazole, methionine, methocarbamol, methotrexate, methoxsalen, methoxyflurane, methsuximide, methyclothiazide, methylbenzethonium chloride, methyldopa, methylergonovine maleate, methylphenidate hydrochloride, methylprednisolone, methyltestosterone, methysergide maleate, metoclopramide, metolazone, meoprolol tartrate, metronidazole, metyrapone, metyrosine, mexiletine hydrochloride, mexiletine hydrochloride, miconazole, minocycline hydrochloride, minoxidil, mitomycin, mitotane, molindone hydrochloride, monobenzone, morphine sulfate, mupirocin, medazepam, mefruside, methandrostenolone, methylsulfadiazine, nadolol, nafcillin, nafcillin sodium, nalidixic acid, nalorphine, naloxone, nandrolone decanoate, nandrolone phenpropionate, naproxen, natamycin, neomycin, neomycin sulfate, neostimine bromide, niacin, nitrofurantoin, nalidixic acid, nifedipine, nitrazepam, nitrofurantoin, nitroglycerine, nitromerson, nizatidine, nonoxynol 9, norethindrone, norethindrone **acetate,** norfloxacin, norgestrel, nortriptyline hydrochloride, noscapine, novobiocin sodium, nystatin, opium, oxacillin sodium, oxamniquine, oxandrolone, oxazepam, oxprenolol hydrochloride, oxtriphylline, oxybenzone, oxybutynin chloride, oxycodone hydrochloride, oxycodone, oxymetazoline hydrochloride, oxymetholone, oxymorphone hydrochloride, oxyphenbutazone, oxytetracycline, padimate, panreatin, pancrelipase, papain, panthenol, papaverin hydrochloride, parachlorophenol, paramethasone **acetate,** paregoric, paromomycin sulfate, penicillamine, penicillin, penicillin derivatives, pentaerythritol tetranitrate, pentazocine, pentazocine hydrochloride, pentazocine salts, pentobarbital sodium, perphenazine, pertussis, phenacemide, phenazopyridine hydrochloride, phendimetrazine tartrate, phenelzine sulfate, phenmetrazine hydrochloride, phenobarbital, phenophtalein, phenoxybenzamine hydrochloride, phentermine hydrochloride, phenylalanine, phenylbutazone, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, physostigmine, phytonadione, pilocarpine , pimozide, pindolol, piperazine, piroxicam plicamycin, poliovirus vaccine inactivated, polycarbophil, polymycin b sulfate, polythiazide, potassium chloride, potassium citrate, potassium cluconate, potassium iodine, potassium sodium tartrate, povidone iodine, pralidoxime chloride, pramoxine hydrochloride, pramezam, prazepam, praziquantel, prazosin hydrochloride, prazosin hydrochloride, prednisolone, prilocaine, primaquine, primidone, probenecid, probucol, procainamide hydrochlorid, procaine hydrochloride, procarbacine hydrochloride, prochlorperazine, prochlorperazine maleate, procyclidine hydrochloride, progesterone, proline, promazine, promazine hydrochloride, promazine, promethazine, promethazine hydrochloride, propafenone hydrochloride, propantheline, proparacaine hydrochloride, propoxycaine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, propanolol hydrochloride, propyliodone, propylthiouracil, propylthiouracil, protriptyline hydrochloride, pseudoephedrine hydrochloride, pumice, pyrantel pamoate, pyrazinamide, pyrethrum extract, pyridostigmine bromide, pyridoxine hydrochloride, pyrilamine maleate, pyrimethamine, pyroxylin, pyrvinium pamoate, phenacetin, phenytoin, prednisone, uinidine gluconate, quinidine sulfate, rabies vaccine, racepinephrine ranitidine, rauwolfia serpentina, resorcinol, ribavirin, riboflavin, rifampin, ritodrine, rubella virus vaccine, saccharin, saccharin sodium, salicylamide, salicylic acid, salsalata, scopolamine, secobarbital sodium, selenius acid, selenium sulfate, sennaserine, simethicone, sodium ascorbate, sodium bicarbonate, sodium fluoride, sodium gluconate, sodium

iodide, sodium lactate, sodium nitrite, sodium ditroprusside, sodium salicylate, spironolactone, stannozolol, streptomycin, sucralfate, sulfacetamide, sulfadiazine, reserpine, sulfadioxine, sulfamerazine, sulfamethazine, sulfamethizole, sulfamethoxazole, sulfamethoxydiazine, sulfapyridin, sulfasalazine, sulfaperin, sulfathiazole, sulfisoxazole, sulfinpyrazone, sulindac, suprofen, stilains, tamoxifen citrate, temacepam, terbutaline sulfate, terfenadine, terpin, testolacton, testosterone, tolazamide, tolbutamide, tetracaine, tetracycline, tetrahydrocycline, theophylline, thiabendazole, thiamine hydrochloride, thiamin, thiamylal, thiethylperazine thimerosal, thioguanine , thioridazine hydrochloride, thistrepton, thiotepa, thiothixene, threonine, thyroid, ticarcillin, timolol, tioconazole, titaniumdioxide, tolazamide, tolbutamide, tolmetin, tolnaftate, trazodone hydrochloride, tretinoin, triacetin, triamcinolone, triamterene, triazolam, trichorfon, trichlormethiazide, trientine hydrochloride, trifluoperazine hydrochloride, triflupromazine, trihexyphenidyl hydrochloride, trimeprazine tartrate, trimethadione, trimethobenzamide hydrochloride, trimethoprim, trioxsalen, tripelennamine, triprolidine, trisulfapyrimidine, tropicamide, trypsin, tryptohan, tuberculin, tyloxapol, tyropanoate sodium, tyrosine, tyrothricin, thyrothricin bethamethasone, thiotic acid, sotalol, salbutamol, norfenefrine, silymarin, dihydroergotamine, buflomedil, etofibrate, indometacin, urea, valine, valproic acid, vancomycin hydrochloride, vasopressin, verapramil, vidarabine, vinblastine, vincristine, vitamins, warfarin, yellow fever vaccine, zinc **acetate,** zinc carbonate, zinc chloride, zinc gluconate, beta acetyl digoxin, piroxicam, haloperidol, ISMN, amitriptylin, diclofenac, nifedipine, verapamil, pyritinol, nitrendipin, doxycycline, bromhexine, methylprdnisolone, clonidine, fenofibrate, allopurinol, pirenyepine, levothyroxin, tamoxifen, metildigoxin, o-(beta-hydroxyethyl)-rutoside, propicillin, aciclovir mononitrate, paracetamol, naftidrofuryl, pentoxifylline, propafenone, acebutolol, L-thyroxin, tramadol, bromocriptine, loperamide, ketotifen, fenoterol, cadobelisate, propanolol, enalaprilhydrogen maleate, bezafebrate, ISDN, gallopamil, xantinol nicotinate, digitoxin, flunitrazepam, bencyclane, dexapanthenol, pindolol, lorazepam, diltiazem, piracetam, phenoxymethylpenicillin, furosemide, bromazepam, flunarizin, erythromycin, metoclopramide, acemetacin, ranitidin, biperiden, metamizole, doxepin, dipotassium chloroazepate, tetrazepam, estramustine phosphate, terbutaline, captopril, maprotiline, prazosin, atenolol, glibenclamide, cefaclor, etilfrine, cimetidine, theophylline, hydromorphone, ibuprofen, primidone, clobazam, oxaceprol, medroxyprogesterone, flecainid, pyridoxal 5 phosphate glutaminate, hymechromone, etofylline clofibrate, vincamine, cinnarizine, diazepam, ketoprofen, flupentixol, molsimine, glibornuride, dimetinden, melperone, soquinolol, dihydrocodeine, clomethiazole, clemastine, glisoxepide, kallidinogenase, oxyfedrine, baclofen, carboxymethylcysteine, thioridazine, betahistine, L-tryptophan, murtol, bromelaine, prenylamine, salazosulfapyridine, astemizol, sulpiride, benzerazide, dibenzepine, acetylsalicylic acid, miconazol, nystatin, ketoconazole, sodium picosulfate, coltyramine, gemfibrocil, rifampicin, fluocortolone, mexiletin, amoxicillin, terfenadrin, mucopolysaccharide polysulfade, triazolam, mianserin, tiaprofenic acid, amezinium metilsulfate, mefloquine, probucol, quinidine, carbamazepine, L-aspartate, penbutolol, piretanide, aescin amitriptyline, cyproterone, sodium valproinate, mebeverine, bisacodyl, 5-aminosalicylic acid, dihydralazine, magaldrate, phenprocoumon, amantadine, naproxen, carteolol, famotidine, methyldopa, auranofine, estriol, nadolol, levomepromazine, doxorubicin,

medofenoxate, azathioprine, flutamide, norfloxacin, fendiline, prajmalium bitartrate, lipid derivatives of phosphonatides, amphiphilic polymers, adenosine derivatives, sulfated tannins, monoclonal antibodies, and metal complexes of water soluble texathyrin.

Other Reference Publication - OREF (1):
Per Artusson et al., "Characterization of Polyacryl Starch Microparticles as Carriers for Proteins and Drugs," Journal of Pharmaceutical Science, vol. 73, No. 11, **pps.** 1507-1513 (Nov. 1984).

Other Reference Publication - OREF (2):
Lennart Randen et al., "Coprecipitation of Enzymes with Water Soluble Starch--An Alternative to Freeze-drying," J. Pharm. Pharmacol., vol. 40, **pps.** 763-766 (1988).

Other Reference Publication - OREF (3):
Shigeaki Maruo et al., "Effects of Moranoline, 4-O-.alpha.-D-Glucopyranosylmoranoline and Their N-Substituted Derivatives on Thermostability of Cyclodextrin Glycosyltransferase, Glucoamylase, and .beta.-Amylase," Biosci. Biotech. Biochem., vol. 57, No. 8, **pps.** 1294-1298, (1993).

Other Reference Publication - OREF (4):
Wendell Q. Sun et al., "Protein stability in the amorphous carbohydrate matrix: relevance to anhydrobiosis," Biochimica et Biophysica Acta, vol. 1425, **pps.** 245-254 (1998).

Other Reference Publication - OREF (5):
Colonna et al., "Extrustion Cooking of Starch & Starchy Products," Extrusion Cooking, C. Mercier, et al. AACC, St. Paul, MN (1989), **pps.** 247-319.

Other Reference Publication - OREF (6):
Meuser et al., "A Systems Analytical Approach To Extrusion," Food Extrusion Science & Technology, ed. J. Kokini, Dekker Publ. (1992), **pps.** 619-630.

US-PAT-NO: 6194457

DOCUMENT-IDENTIFIER: US 6194457 B1
See image for Certificate of Correction

TITLE: Liquid eye drop composition

DATE-ISSUED: February 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Braswell; A. Glenn	Marine del Rey	GA	90292	N/A
Absher; Kenneth J.	Carson City	NV	89703	N/A
Duarte; Alex	Nevada City	CA	95959	N/A

APPL-NO: 09/ 015755

DATE FILED: January 29, 1998

PARENT-CASE:

This nonprovisional application claims the benefit of U.S. Provisional Application No. 06/036,516, filed Jan. 29, 1997.

US-CL-CURRENT: 514/547, 514/561 , 514/562 , 514/912

ABSTRACT:

A composition that is used as an eye treatment contains reduced glutathione, vitamin A and vitamin E, as well as one or more of zinc sulfate, boric acid and potassium as buffering agents. The composition also may contain a lubricant and a preservative. The composition is a sterile isotonic solution. The composition is used in a method of treating eyes for the alleviation of irritations and/or dryness, as well as for the prevention and treatment of cataracts.

20 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Brief Summary Text - BSTX (7):

Light entering the eye permits the generation of free radicals within the lens, in particular the superoxide radical O.sub.2.sup.-, which in turn can degenerate into other free radicals such as hydrogen peroxide and hydroxide radicals. These free radicals act to oxidize the proteins of the lens. Oxidation of the proteins is known to be a major factor leading to the onset of

cataracts, which is a loss of transparency of the lens. See, for example, Varma, "Scientific Basis for Medical Therapy of Cataracts by Antioxidants", Am. S. Clin. Nutr., vol. 53, **pps**. 335S-345S (1991).

Brief Summary Text - BSTX (8):

Accordingly, the lens of the eye has an antioxidant defense system to respond to an oxidative stress and maintain the integrity of the lens. Various studies have shown that the antioxidant defense system includes the enzymes glutathione peroxidase, catalase and superoxide dismutase, and the antioxidants vitamin A (ascorbic acid), vitamin E (.alpha.-tocopherol) and .beta.-**carotene**. See, for example, Kamei, "Glutathione Levels of the Human Crystalline Lens in Aging", Biol. Pharm. Bull., vol. 16, no. 9, **pps**. 870-875 (1993); Fletcher et al., "Glutathione and Aging: Ideas and Evidence", The Lancet, vol. 344, **pps**. 1379-1380 (1994); and Jacques et al., "Antioxidant Status in Persons With and Without Senile Cataracts", Arch. Opthalmol., vol. 106, **pps**. 337-340 (1988).

Brief Summary Text - BSTX (9):

The role of each of the above materials in protecting the lens against degradation by oxidation has also been widely studied. Most studies have focused upon dietary supplementation of the materials to preserve the antioxidant defense system of the lens during aging, thus preventing or slowing the onset of cataracts. See, for example, Robertson et al., "Vitamin E Intake and Risk of Cataracts in Humans", Annals New York Academy of Sciences, **pps**. 372-382; "Protective Role of Vitamin E in Cataract Development", Vitamin E Research Information Service (1990); Devamanoharan et al., "Prevention of Selenite Cataract by Vitamin C", Exp. Eye Res., vol. 52, **pps**. 563-568 (1991); and Jacques et al., "Epidemiologic Evidence of a Role for the Antioxidant Vitamins and Cartenoids in Cataract Prevention", Am. J. Clin. Nutr., vol. 53, **pps**. 352S-355S (1991). See also U.S. Pat. No. 5,075,116 to LaHaye et al.

Brief Summary Text - BSTX (10):

Studies have also confirmed that the materials vitamin A, vitamin E and glutathione have a close interaction in regenerating one another following oxidation of one or more of these molecules. See, for example, Stoyanovsky et al., "Endogenous Ascorbate Regenerates Vitamin E in the Retina Directly and in Combination With Exogenous Dihydrolipoic Acid", Current Eye Research (1994); and Winkler et al., "The Redox Couple Between Glutathione and Ascorbic Acid: A Chemical and Physiological Perspective", Free Radical Biology & Medicine, vol. 17, no. 4, **pps**. 333-349 (1994).

Brief Summary Text - BSTX (11):

A role has also been reported for zinc and copper in maintenance of retinal metabolism. See Hirayama, "Histochemical Localization of Zinc and Copper in Rat Ocular Tissues", Acta Histochem., vol. 89, **pps**. 107-111 (1990). Zinc has been cited as a cofactor for several antioxidant systems present in the retinal pigment epithelium. See Newsome et al., "Zinc Uptake by Primate Retinal Pigment Epithelium and Choroid", Current Eye Research, vol. 11, no. 3, **pps**. 213-217 (1992).

Brief Summary Text - BSTX (27):

The eye treatment composition of the invention is a solution preferably having a vehicle of water, preferably deionized water, or mixtures of water and water-miscible solvents such as, for example, lower alkanols or arylalkanols, phosphate buffer vehicle systems, isotonic vehicles such as boric acid, sodium chloride, sodium citrate, sodium **acetate** and the like, vegetable oils, polyalkylene glycols, and petroleum based jelly, as well as aqueous solutions containing ethyl cellulose, carboxymethyl cellulose and derivatives thereof, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, carbopol, polyvinyl alcohol, polyvinyl pyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The aqueous-based vehicle comprises the balance of the eye drop composition.

US-PAT-NO: 6130321

DOCUMENT-IDENTIFIER: US 6130321 A

TITLE: High tap density chitosan, and methods of production

DATE-ISSUED: October 10, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnson; Edwin Lee	Issaquah	WA	N/A	N/A
Nichols; Everett Junior	Edmonds	WA	N/A	N/A

APPL-NO: 09/ 114023

DATE FILED: July 10, 1998

US-CL-CURRENT: 536/20

ABSTRACT:

The present invention provides novel methods of producing chitosan having a tap density of at least about 0.4 g/ml. In one aspect of the present invention, chitosan is selected having an average molecular mass of from about one thousand Daltons to about two million Daltons; a particle size that is smaller than 20 mesh; a viscosity of at least about 1 cps, and a percentage of deacetylation of from about 65% to about 98% A measured amount of the selected chitosan is then mixed with an amount of water that is from about two to about ten times the weight of the chitosan, and an amount of an acid that is at least about 0.1% of the weight of the chitosan. The acid is preferably an organic acid. The mixture of chitosan, water and acid is then mixed to a smooth paste, dried to a moisture content of from 0% moisture to about 20% moisture, and the particle size is preferably reduced to smaller than 20 mesh. In another aspect of the invention, chitosan is provided having a tap density of at least about 0.4 g/ml and the ability to freely flow through an orifice having a circular cross section having a diameter of about 4 mm. The chitosan of the present invention is relatively odorless.

34 Claims, 4 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 4

---------- KWIC ---------

Brief Summary Text - BSTX (6):

With respect to the use of chitosan as a dietary supplement, chitosan is

often used to reduce the blood serum level of cholesterol, and to promote weight loss by impeding dietary fat absorption in the gastrointestinal tract. Chitosan can be encapsulated or tabletized either alone or in combination with other ingredients including vitamins C, E, B6, .beta.-carotene, folic acid, and a variety of binders. For the benefit of those individuals who have difficulty swallowing tablets or capsules, chitosan can be added to baked goods, such as crackers, cookies and cakes, and to beverages. Again, a high density preparation of chitosan is desirable because, for example, a smaller volume of high density chitosan need be consumed, compared to standard, lower density chitosan, in order to deliver the same dose of chitosan. Thus, for example, a person need consume fewer tablets or capsules of high density chitosan compared to standard preparations of lower density chitosan.

Claims Text - CLTX (41):

33. Chitosan of claim 23 wherein said chitosan is selected from the group consisting of chitosan succinate, chitosan adipate, chitosan chloride, chitosan glutamate, chitosan lactate, chitosan aspartate, chitosan acetate, chitosan pyruvate, and chitosan malate.

Claims Text - CLTX (42):

34. Chitosan of claim 27 wherein said chitosan is selected from the group consisting of chitosan succinate, chitosan adipate, chitosan chloride, chitosan glutamate, chitosan lactate, chitosan aspartate, chitosan acetate, chitosan pyruvate, and chitosan malate.

Other Reference Publication - OREF (1):

T. Yui et al., "Molecular and Crystal Structure of the Anhydrous Form of Chitosan", Macromolecules, vol. 27, pps. 7601-7605, (Dec. 1994).

Other Reference Publication - OREF (2):

G. G. Allan, M. Peyron, "Molecular weight manipulation of chitosan I: kinetics of depolymerization by nitruos acid", Carbohydrate Research, vol. 277, pps. 257-272 (1995) month not available.

Other Reference Publication - OREF (3):

J. Li, J.F. Revol and R.H. Marchessault, Effect of Degree of Deacetylation of Chitin on the Properties of Chitin Crystallites, John Wiley & Sons, Inc. ccc 0021-8995/97/020373-08., pps. 373-380 (1997) month not available.

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FILE 'HOME' ENTERED AT 15:29:16 ON 17 JUN 2003

=> fil .bec
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY     SESSION
FULL ESTIMATED COST                                         6.93        6.93

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 15:48:52 ON 17 JUN 2003
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

11 FILES IN THE FILE LIST

=> s glnap?
FILE 'MEDLINE'
L1            54 GLNAP?

FILE 'SCISEARCH'
L2            35 GLNAP?

FILE 'LIFESCI'
L3            49 GLNAP?

FILE 'BIOTECHDS'
L4             5 GLNAP?

FILE 'BIOSIS'
L5            56 GLNAP?

FILE 'EMBASE'
L6            45 GLNAP?

FILE 'HCAPLUS'
L7            62 GLNAP?

FILE 'NTIS'
L8             0 GLNAP?

FILE 'ESBIOBASE'
L9            22 GLNAP?

FILE 'BIOTECHNO'
L10           43 GLNAP?

FILE 'WPIDS'
L11            2 GLNAP?

TOTAL FOR ALL FILES
L12          373 GLNAP?

=> s acetyl phosphate or acetylphosphate or acetate
FILE 'MEDLINE'
         37019 ACETYL
        123587 PHOSPHATE
           324 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
            71 ACETYLPHOSPHATE
         85997 ACETATE
L13      86292 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'SCISEARCH'
         36635 ACETYL
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```
         127161 PHOSPHATE
            311 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             34 ACETYLPHOSPHATE
          83662 ACETATE
L14       83932 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'LIFESCI'
          10624 "ACETYL"
          36365 "PHOSPHATE"
            166 ACETYL PHOSPHATE
                  ("ACETYL"(W)"PHOSPHATE")
             22 ACETYLPHOSPHATE
          23165 ACETATE
L15       23300 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'BIOTECHDS'
           2604 ACETYL
          15692 PHOSPHATE
             48 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             11 ACETYLPHOSPHATE
          11055 ACETATE
L16       11080 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'BIOSIS'
          83598 ACETYL
         186290 PHOSPHATE
            422 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             78 ACETYLPHOSPHATE
         112682 ACETATE
L17      113043 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'EMBASE'
          38373 "ACETYL"
         151764 "PHOSPHATE"
            265 ACETYL PHOSPHATE
                  ("ACETYL"(W)"PHOSPHATE")
             40 ACETYLPHOSPHATE
          99814 ACETATE
L18      100043 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'HCAPLUS'
         133024 ACETYL
         482852 PHOSPHATE
            925 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
            236 ACETYLPHOSPHATE
         449406 ACETATE
L19      450162 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'NTIS'
            725 ACETYL
           6281 PHOSPHATE
              1 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
              1 ACETYLPHOSPHATE
           3039 ACETATE
L20        3039 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'ESBIOBASE'
          11210 ACETYL
          35348 PHOSPHATE
```

```
            135 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             16 ACETYLPHOSPHATE
          22040 ACETATE
L21       22163 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'BIOTECHNO'
          11762 ACETYL
          48786 PHOSPHATE
            184 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             28 ACETYLPHOSPHATE
          28164 ACETATE
L22       28325 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'WPIDS'
          23959 ACETYL
          79708 PHOSPHATE
             31 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             17 ACETYLPHOSPHATE
         109139 ACETATE
L23      109165 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

TOTAL FOR ALL FILES
L24     1030544 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

=> s promoter?
FILE 'MEDLINE'
L25       98850 PROMOTER?

FILE 'SCISEARCH'
L26      101706 PROMOTER?

FILE 'LIFESCI'
L27       58126 PROMOTER?

FILE 'BIOTECHDS'
L28       27161 PROMOTER?

FILE 'BIOSIS'
L29      110649 PROMOTER?

FILE 'EMBASE'
L30       82138 PROMOTER?

FILE 'HCAPLUS'
L31      153849 PROMOTER?

FILE 'NTIS'
L32        1487 PROMOTER?

FILE 'ESBIOBASE'
L33       52200 PROMOTER?

FILE 'BIOTECHNO'
L34       71268 PROMOTER?

FILE 'WPIDS'
L35       28369 PROMOTER?

TOTAL FOR ALL FILES
L36      785803 PROMOTER?
```

```
=> s l12 and (l24 or l36(8a)(induc? or regulat? or activat? or modulat?))
FILE 'MEDLINE'
       1409841 INDUC?
        617895 REGULAT?
        612120 ACTIVAT?
        177205 MODULAT?
         26673 L25(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L37         32 L1 AND (L13 OR L25(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'SCISEARCH'
       1280733 INDUC?
        531767 REGULAT?
        662571 ACTIVAT?
        254318 MODULAT?
         27369 L26(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L38         24 L2 AND (L14 OR L26(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'LIFESCI'
        365306 INDUC?
        216162 REGULAT?
        196755 ACTIVAT?
         65773 MODULAT?
         19111 L27(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L39         30 L3 AND (L15 OR L27(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'BIOTECHDS'
         34401 INDUC?
         21620 REGULAT?
         20686 ACTIVAT?
          8840 MODULAT?
          5161 L28(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L40          4 L4 AND (L16 OR L28(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'BIOSIS'
       1312404 INDUC?
        677816 REGULAT?
        630593 ACTIVAT?
        208034 MODULAT?
         33110 L29(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L41         37 L5 AND (L17 OR L29(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'EMBASE'
       1073075 INDUC?
        509427 REGULAT?
        534507 ACTIVAT?
        170139 MODULAT?
         25027 L30(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L42         29 L6 AND (L18 OR L30(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'HCAPLUS'
       1743421 INDUC?
        766708 REGULAT?
       1054351 ACTIVAT?
        264423 MODULAT?
         42072 L31(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L43         45 L7 AND (L19 OR L31(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))
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FILE 'NTIS'
         66942 INDUC?
         80764 REGULAT?
         27469 ACTIVAT?
         20991 MODULAT?
           243 L32(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L44          0 L8 AND (L20 OR L32(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'ESBIOBASE'
        396356 INDUC?
        290001 REGULAT?
        235886 ACTIVAT?
         81816 MODULAT?
         17806 L33(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L45         16 L9 AND (L21 OR L33(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'BIOTECHNO'
        314104 INDUC?
        250585 REGULAT?
        216020 ACTIVAT?
         53769 MODULAT?
         22485 L34(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L46         27 L10 AND (L22 OR L34(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULA
               T?))

FILE 'WPIDS'
        218634 INDUC?
        335753 REGULAT?
        219138 ACTIVAT?
        137137 MODULAT?
          3806 L35(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L47          2 L11 AND (L23 OR L35(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULA
               T?))

TOTAL FOR ALL FILES
L48        246 L12 AND (L24 OR L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULA
               T?))

=> s l24(8a)l36(8a)(induc? or regulat? or activat? or modulat?)
FILE 'MEDLINE'
       1409841 INDUC?
        617895 REGULAT?
        612120 ACTIVAT?
        177205 MODULAT?
L49        571 L13(8A)L25(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'SCISEARCH'
       1280733 INDUC?
        531767 REGULAT?
        662571 ACTIVAT?
        254318 MODULAT?
L50        373 L14(8A)L26(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'LIFESCI'
        365306 INDUC?
        216162 REGULAT?
        196755 ACTIVAT?
         65773 MODULAT?
L51        238 L15(8A)L27(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'BIOTECHDS'
         34401 INDUC?
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          21620 REGULAT?
          20686 ACTIVAT?
           8840 MODULAT?
L52           7 L16(8A)L28(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'BIOSIS'
        1312404 INDUC?
         677816 REGULAT?
         630593 ACTIVAT?
         208034 MODULAT?
L53         695 L17(8A)L29(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'EMBASE'
        1073075 INDUC?
         509427 REGULAT?
         534507 ACTIVAT?
         170139 MODULAT?
L54         578 L18(8A)L30(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'HCAPLUS'
        1743421 INDUC?
         766708 REGULAT?
        1054351 ACTIVAT?
         264423 MODULAT?
L55         583 L19(8A)L31(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'NTIS'
          66942 INDUC?
          80764 REGULAT?
          27469 ACTIVAT?
          20991 MODULAT?
L56           3 L20(8A)L32(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'ESBIOBASE'
         396356 INDUC?
         290001 REGULAT?
         235886 ACTIVAT?
          81816 MODULAT?
L57         189 L21(8A)L33(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'BIOTECHNO'
         314104 INDUC?
         250585 REGULAT?
         216020 ACTIVAT?
          53769 MODULAT?
L58         344 L22(8A)L34(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'WPIDS'
         218634 INDUC?
         335753 REGULAT?
         219138 ACTIVAT?
         137137 MODULAT?
L59           7 L23(8A)L35(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

TOTAL FOR ALL FILES
L60        3588 L24(8A) L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

=> s l60 not ((phorbol or tetradecanoylphorbol)(2a)acetate)
FILE 'MEDLINE'
          31032 PHORBOL
          26725 TETRADECANOYLPHORBOL
          85997 ACETATE
          30437 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L61          35 L49 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)
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FILE 'SCISEARCH'
         29522 PHORBOL
          4491 TETRADECANOYLPHORBOL
         83662 ACETATE
         11169 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L62         84 L50 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'LIFESCI'
         11370 PHORBOL
          2294 TETRADECANOYLPHORBOL
         23165 ACETATE
          5584 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L63         48 L51 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'BIOTECHDS'
           274 PHORBOL
            47 TETRADECANOYLPHORBOL
         11055 ACETATE
           149 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L64          2 L52 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'BIOSIS'
         37478 PHORBOL
          9328 TETRADECANOYLPHORBOL
        112682 ACETATE
         21297 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L65        112 L53 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'EMBASE'
         36797 PHORBOL
          5982 TETRADECANOYLPHORBOL
         99814 ACETATE
         24891 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L66         45 L54 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'HCAPLUS'
         30927 PHORBOL
          6318 TETRADECANOYLPHORBOL
        449406 ACETATE
         15765 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L67        134 L55 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'NTIS'
           194 PHORBOL
            29 TETRADECANOYLPHORBOL
          3039 ACETATE
            80 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L68          0 L56 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'ESBIOBASE'
         10955 PHORBOL
          1968 TETRADECANOYLPHORBOL
         22040 ACETATE
          4576 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L69         55 L57 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'BIOTECHNO'
         18056 PHORBOL
          3163 TETRADECANOYLPHORBOL
         28164 ACETATE
         11969 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L70         37 L58 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)
```

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FILE 'WPIDS'
           288 PHORBOL
            40 TETRADECANOYLPHORBOL
        109139 ACETATE
           137 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L71          4 L59 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

TOTAL FOR ALL FILES
L72        556 L60 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE)

=> s pps or phosphoenol pyruvate synthase#
FILE 'MEDLINE'
          2102 PPS
           226 PHOSPHOENOL
         23415 PYRUVATE
         71030 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L73       2102 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'SCISEARCH'
          1957 PPS
           220 PHOSPHOENOL
         18316 PYRUVATE
         80480 SYNTHASE#
             1 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L74       1958 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'LIFESCI'
           328 PPS
           114 "PHOSPHOENOL"
          5779 "PYRUVATE"
         19700 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
                 ("PHOSPHOENOL"(W)"PYRUVATE"(W)SYNTHASE#)
L75        328 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'BIOTECHDS'
           107 PPS
           104 PHOSPHOENOL
          1784 PYRUVATE
          4448 SYNTHASE#
            21 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L76        108 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'BIOSIS'
          1096 PPS
          3651 PHOSPHOENOL
         34782 PYRUVATE
         78919 SYNTHASE#
            11 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L77       1104 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'EMBASE'
          1381 PPS
           173 "PHOSPHOENOL"
         19215 "PYRUVATE"
         69481 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
                 ("PHOSPHOENOL"(W)"PYRUVATE"(W)SYNTHASE#)
L78       1381 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#
```

```
FILE 'HCAPLUS'
          2657 PPS
           676 PHOSPHOENOL
         46724 PYRUVATE
         72314 SYNTHASE#
             7 PHOSPHOENOL PYRUVATE SYNTHASE#
               (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L79       2662 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'NTIS'
           689 PPS
             5 PHOSPHOENOL
           304 PYRUVATE
           202 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
               (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L80        689 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'ESBIOBASE'
           419 PPS
            72 PHOSPHOENOL
          5427 PYRUVATE
         31769 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
               (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L81        419 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'BIOTECHNO'
           231 PPS
            77 PHOSPHOENOL
          6261 PYRUVATE
         27132 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
               (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L82        231 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'WPIDS'
          1273 PPS
           166 PHOSPHOENOL
          1620 PYRUVATE
          3209 SYNTHASE#
            24 PHOSPHOENOL PYRUVATE SYNTHASE#
               (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L83       1275 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

TOTAL FOR ALL FILES
L84      12257 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

=> s l84(5a)gene/q
FILE 'MEDLINE'
L85         39 L73(5A)GENE/Q

FILE 'SCISEARCH'
L86         40 L74(5A)GENE/Q

FILE 'LIFESCI'
L87         27 L75(5A)GENE/Q

FILE 'BIOTECHDS'
L88         37 L76(5A)GENE/Q

FILE 'BIOSIS'
L89         54 L77(5A)GENE/Q
```

```
FILE 'EMBASE'
L90          36 L78(5A)GENE/Q

FILE 'HCAPLUS'
L91         111 L79(5A)GENE/Q

FILE 'NTIS'
L92           1 L80(5A)GENE/Q

FILE 'ESBIOBASE'
L93          27 L81(5A)GENE/Q

FILE 'BIOTECHNO'
L94          28 L82(5A)GENE/Q

FILE 'WPIDS'
L95          43 L83(5A)GENE/Q

TOTAL FOR ALL FILES
L96         443 L84(5A) GENE/Q

=> s phosphoenolpyruvate synthase#
FILE 'MEDLINE'
          6307 PHOSPHOENOLPYRUVATE
         71030 SYNTHASE#
L97         27 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'SCISEARCH'
          5812 PHOSPHOENOLPYRUVATE
         80480 SYNTHASE#
L98         25 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'LIFESCI'
          2113 "PHOSPHOENOLPYRUVATE"
         19700 SYNTHASE#
L99         16 PHOSPHOENOLPYRUVATE SYNTHASE#
                 ("PHOSPHOENOLPYRUVATE"(W)SYNTHASE#)

FILE 'BIOTECHDS'
           433 PHOSPHOENOLPYRUVATE
          4448 SYNTHASE#
L100        12 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'BIOSIS'
          7639 PHOSPHOENOLPYRUVATE
         78919 SYNTHASE#
L101        43 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'EMBASE'
          4238 "PHOSPHOENOLPYRUVATE"
         69481 SYNTHASE#
L102        23 PHOSPHOENOLPYRUVATE SYNTHASE#
                 ("PHOSPHOENOLPYRUVATE"(W)SYNTHASE#)

FILE 'HCAPLUS'
         10663 PHOSPHOENOLPYRUVATE
         72314 SYNTHASE#
L103       107 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)
```

```
FILE 'NTIS'
            37 PHOSPHOENOLPYRUVATE
           202 SYNTHASE#
L104         1 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'ESBIOBASE'
          1799 PHOSPHOENOLPYRUVATE
         31769 SYNTHASE#
L105        14 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'BIOTECHNO'
          2400 PHOSPHOENOLPYRUVATE
         27132 SYNTHASE#
L106        21 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'WPIDS'
           200 PHOSPHOENOLPYRUVATE
          3209 SYNTHASE#
L107         6 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

TOTAL FOR ALL FILES
L108       295 PHOSPHOENOLPYRUVATE SYNTHASE#

=> s l108(5a)gene/q
FILE 'MEDLINE'
L109         3 L97 (5A)GENE/Q

FILE 'SCISEARCH'
L110         5 L98 (5A)GENE/Q

FILE 'LIFESCI'
L111         4 L99 (5A)GENE/Q

FILE 'BIOTECHDS'
L112         4 L100(5A)GENE/Q

FILE 'BIOSIS'
L113        12 L101(5A)GENE/Q

FILE 'EMBASE'
L114         5 L102(5A)GENE/Q

FILE 'HCAPLUS'
L115        40 L103(5A)GENE/Q

FILE 'NTIS'
L116         0 L104(5A)GENE/Q

FILE 'ESBIOBASE'
L117         5 L105(5A)GENE/Q

FILE 'BIOTECHNO'
L118         5 L106(5A)GENE/Q

FILE 'WPIDS'
L119         2 L107(5A)GENE/Q

TOTAL FOR ALL FILES
L120        85 L108(5A) GENE/Q
```

```
=> s (l96 or l120) and l24
FILE 'MEDLINE'
L121          2 (L85 OR L109) AND L13

FILE 'SCISEARCH'
L122          2 (L86 OR L110) AND L14

FILE 'LIFESCI'
L123          1 (L87 OR L111) AND L15

FILE 'BIOTECHDS'
L124          1 (L88 OR L112) AND L16

FILE 'BIOSIS'
L125          3 (L89 OR L113) AND L17

FILE 'EMBASE'
L126          2 (L90 OR L114) AND L18

FILE 'HCAPLUS'
L127          5 (L91 OR L115) AND L19

FILE 'NTIS'
L128          0 (L92 OR L116) AND L20

FILE 'ESBIOBASE'
L129          0 (L93 OR L117) AND L21

FILE 'BIOTECHNO'
L130          2 (L94 OR L118) AND L22

FILE 'WPIDS'
L131          2 (L95 OR L119) AND L23

TOTAL FOR ALL FILES
L132         20 (L96 OR L120) AND L24

=> s (l96 or l120)(5a)(overexpress? or amplif? or increas?)
FILE 'MEDLINE'
         46356 OVEREXPRESS?
         80503 AMPLIF?
       1739744 INCREAS?
L133          0 (L85 OR L109)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'SCISEARCH'
         53088 OVEREXPRESS?
        127002 AMPLIF?
       1690246 INCREAS?
L134          0 (L86 OR L110)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'LIFESCI'
         21016 OVEREXPRESS?
         40050 AMPLIF?
        448377 INCREAS?
L135          0 (L87 OR L111)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'BIOTECHDS'
          2961 OVEREXPRESS?
         23969 AMPLIF?
         54438 INCREAS?
L136          1 (L88 OR L112)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'BIOSIS'
```

```
         51984 OVEREXPRESS?
        112383 AMPLIF?
       1890845 INCREAS?
L137          2 (L89 OR L113)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'EMBASE'
         43945 OVEREXPRESS?
         72465 AMPLIF?
       1642174 INCREAS?
L138          0 (L90 OR L114)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'HCAPLUS'
         47258 OVEREXPRESS?
        139970 AMPLIF?
       3493575 INCREAS?
L139         32 (L91 OR L115)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'NTIS'
           663 OVEREXPRESS?
         17648 AMPLIF?
        177108 INCREAS?
L140          0 (L92 OR L116)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'ESBIOBASE'
         33672 OVEREXPRESS?
         41555 AMPLIF?
        565029 INCREAS?
L141          0 (L93 OR L117)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'BIOTECHNO'
         32854 OVEREXPRESS?
         64034 AMPLIF?
        359617 INCREAS?
L142          0 (L94 OR L118)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'WPIDS'
          1692 OVEREXPRESS?
        228214 AMPLIF?
       1100016 INCREAS?
L143          0 (L95 OR L119)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

TOTAL FOR ALL FILES
L144         35 (L96 OR L120)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

=> s (148 or 172 or 1132 or 1144) not 2001-2003/py
FILE 'MEDLINE'
       1259962 2001-2003/PY
L145         56 (L37 OR L61 OR L121 OR L133) NOT 2001-2003/PY

FILE 'SCISEARCH'
       2305749 2001-2003/PY
L146         89 (L38 OR L62 OR L122 OR L134) NOT 2001-2003/PY

FILE 'LIFESCI'
        223576 2001-2003/PY
L147         70 (L39 OR L63 OR L123 OR L135) NOT 2001-2003/PY

FILE 'BIOTECHDS'
         46337 2001-2003/PY
L148          4 (L40 OR L64 OR L124 OR L136) NOT 2001-2003/PY

FILE 'BIOSIS'
       1215331 2001-2003/PY
L149        134 (L41 OR L65 OR L125 OR L137) NOT 2001-2003/PY
```

```
FILE 'EMBASE'
       1044608 2001-2003/PY
L150         67 (L42 OR L66 OR L126 OR L138) NOT 2001-2003/PY

FILE 'HCAPLUS'
       2417906 2001-2003/PY
L151        154 (L43 OR L67 OR L127 OR L139) NOT 2001-2003/PY

FILE 'NTIS'
         33435 2001-2003/PY
L152          0 (L44 OR L68 OR L128 OR L140) NOT 2001-2003/PY

FILE 'ESBIOBASE'
        671253 2001-2003/PY
L153         54 (L45 OR L69 OR L129 OR L141) NOT 2001-2003/PY

FILE 'BIOTECHNO'
        271276 2001-2003/PY
L154         57 (L46 OR L70 OR L130 OR L142) NOT 2001-2003/PY

FILE 'WPIDS'
       2253073 2001-2003/PY
L155          2 (L47 OR L71 OR L131 OR L143) NOT 2001-2003/PY

TOTAL FOR ALL FILES
L156        687 (L48 OR L72 OR L132 OR L144) NOT 2001-2003/PY

=> save temp l156 pps/a
ANSWER SET L156 HAS BEEN SAVED AS 'PPS/A'

=> fil .becpat
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    15.27      15.48

FILES 'BIOTECHDS, HCAPLUS, WPIDS' ENTERED AT 13:35:32 ON 18 JUN 2003
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

3 FILES IN THE FILE LIST

=> s (L48 OR L72 OR L132 OR L144) and wo/pc range=2001,
FILE 'BIOTECHDS'
             1 GLNAP?
           435 ACETYL
          2853 PHOSPHATE
             4 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
             1 ACETYLPHOSPHATE
          1220 ACETATE
          6659 PROMOTER?
          7986 INDUC?
          7160 REGULAT?
          4931 ACTIVAT?
          5560 MODULAT?
          1513 L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
           435 ACETYL
          2853 PHOSPHATE
             4 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
             1 ACETYLPHOSPHATE
          1220 ACETATE
          6659 PROMOTER?
          7986 INDUC?
```

```
          7160 REGULAT?
          4931 ACTIVAT?
          5560 MODULAT?
             4 L24(8A) L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
            54 PHORBOL
            12 TETRADECANOYLPHORBOL
          1220 ACETATE
            21 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
            47 PPS
            70 PHOSPHOENOL
           373 PYRUVATE
          1221 SYNTHASE#
            21 PHOSPHOENOL PYRUVATE SYNTHASE#
               (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
            24 L84(5A) GENE/Q
           123 PHOSPHOENOLPYRUVATE
          1221 SYNTHASE#
             7 PHOSPHOENOLPYRUVATE SYNTHASE#
               (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)
             2 L108(5A) GENE/Q
           435 ACETYL
          2853 PHOSPHATE
             4 ACETYL PHOSPHATE
               (ACETYL(W)PHOSPHATE)
             1 ACETYLPHOSPHATE
          1220 ACETATE
            47 PPS
            70 PHOSPHOENOL
           373 PYRUVATE
          1221 SYNTHASE#
            21 PHOSPHOENOL PYRUVATE SYNTHASE#
               (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
           123 PHOSPHOENOLPYRUVATE
          1221 SYNTHASE#
             7 PHOSPHOENOLPYRUVATE SYNTHASE#
               (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)
             2 L108(5A) GENE/Q
          1358 OVEREXPRESS?
         12363 AMPLIF?
          9844 INCREAS?
             0 (L96 OR L120)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)
         18816 WO/PC
L157        2 (L48 OR L72 OR L132 OR L144) AND WO/PC

FILE 'HCAPLUS'
             8 GLNAP?
         10297 ACETYL
         38524 PHOSPHATE
            38 ACETYL PHOSPHATE
               (ACETYL(W)PHOSPHATE)
            11 ACETYLPHOSPHATE
         37639 ACETATE
         30651 PROMOTER?
        241456 INDUC?
        131943 REGULAT?
        150909 ACTIVAT?
         52604 MODULAT?
          9951 L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
         10297 ACETYL
         38524 PHOSPHATE
            38 ACETYL PHOSPHATE
               (ACETYL(W)PHOSPHATE)
            11 ACETYLPHOSPHATE
         37639 ACETATE
```

```
          30651 PROMOTER?
         241456 INDUC?
         131943 REGULAT?
         150909 ACTIVAT?
          52604 MODULAT?
             79 L24(8A) L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
           2927 PHORBOL
            546 TETRADECANOYLPHORBOL
          37639 ACETATE
           1321 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
            567 PPS
            134 PHOSPHOENOL
           3064 PYRUVATE
          17391 SYNTHASE#
              4 PHOSPHOENOL PYRUVATE SYNTHASE#
                  (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
             48 L84(5A) GENE/Q
            890 PHOSPHOENOLPYRUVATE
          17391 SYNTHASE#
             48 PHOSPHOENOLPYRUVATE SYNTHASE#
                  (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)
             27 L108(5A) GENE/Q
          10297 ACETYL
          38524 PHOSPHATE
             38 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             11 ACETYLPHOSPHATE
          37639 ACETATE
            567 PPS
            134 PHOSPHOENOL
           3064 PYRUVATE
          17391 SYNTHASE#
              4 PHOSPHOENOL PYRUVATE SYNTHASE#
                  (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
            890 PHOSPHOENOLPYRUVATE
          17391 SYNTHASE#
             48 PHOSPHOENOLPYRUVATE SYNTHASE#
                  (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)
             27 L108(5A) GENE/Q
          16968 OVEREXPRESS?
          32783 AMPLIF?
         372311 INCREAS?
             30 (L96 OR L120)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)
         116278 WO/PC
L158         31 (L48 OR L72 OR L132 OR L144) AND WO/PC

FILE 'WPIDS'
              1 GLNAP?
           2576 ACETYL
          10353 PHOSPHATE
              4 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
              1 ACETYLPHOSPHATE
          11543 ACETATE
           8533 PROMOTER?
          35344 INDUC?
          48515 REGULAT?
          35722 ACTIVAT?
          25328 MODULAT?
           1721 L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
           2576 ACETYL
          10353 PHOSPHATE
              4 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
```

```
            1 ACETYLPHOSPHATE
        11543 ACETATE
         8533 PROMOTER?
        35344 INDUC?
        48515 REGULAT?
        35722 ACTIVAT?
        25328 MODULAT?
            4 L24(8A) L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
          103 PHORBOL
           14 TETRADECANOYLPHORBOL
        11543 ACETATE
           43 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
          210 PPS
           82 PHOSPHOENOL
          502 PYRUVATE
         1457 SYNTHASE#
           23 PHOSPHOENOL PYRUVATE SYNTHASE#
                (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
           29 L84(5A) GENE/Q
          120 PHOSPHOENOLPYRUVATE
         1457 SYNTHASE#
            4 PHOSPHOENOLPYRUVATE SYNTHASE#
                (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)
            1 L108(5A) GENE/Q
         2576 ACETYL
        10353 PHOSPHATE
            4 ACETYL PHOSPHATE
                (ACETYL(W)PHOSPHATE)
            1 ACETYLPHOSPHATE
        11543 ACETATE
          210 PPS
           82 PHOSPHOENOL
          502 PYRUVATE
         1457 SYNTHASE#
           23 PHOSPHOENOL PYRUVATE SYNTHASE#
                (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
          120 PHOSPHOENOLPYRUVATE
         1457 SYNTHASE#
            4 PHOSPHOENOLPYRUVATE SYNTHASE#
                (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)
            1 L108(5A) GENE/Q
         1006 OVEREXPRESS?
        29761 AMPLIF?
       151517 INCREAS?
            0 (L96 OR L120)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)
       248323 WO/PC
L159        2 (L48 OR L72 OR L132 OR L144) AND WO/PC

TOTAL FOR ALL FILES
L160       35 (L48 OR L72 OR L132 OR L144) AND WO/PC

=> dup rem l160
PROCESSING COMPLETED FOR L160
L161       32 DUP REM L160 (3 DUPLICATES REMOVED)

=> d tot

L161  ANSWER 1 OF 32  BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
TI    Method for the production of pyruvate in high conversion and yield,
      comprises carrying out fermentation using microorganisms with reduced or
      eliminated activity of pyruvate decomposing enzymes;
         pyruvic acid preparation by mutant bacterium fermentation
AU    BOTT M; GERHARZ T; TAKORS R; ZELIC B
AN    2003-10747  BIOTECHDS
```

PI **WO** 20030000913 3 Jan 2003

L161 ANSWER 2 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing genes iclR and fadR for fermentative prodn. of threonine
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
IN Rieping, Mechthild; Siebelt, Nicole
AN 2003:356618 HCAPLUS
DN 138:363837

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003038106	A2	20030508	WO 2002-EP10791	20020926 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10154102	A1	20030515	DE 2001-10154102	20011102

L161 ANSWER 3 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli for the fermentative production of threonine containing an attenuated aceK gene
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
IN Hermann, Thomas
AN 2003:76954 HCAPLUS
DN 138:132163

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008616	A2	20030130	WO 2002-EP7353	20020703 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10135051	A1	20030206	DE 2001-10135051	20010718

L161 ANSWER 4 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing genes sucC and sucD for the fermentative production of threonine
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76953 HCAPLUS
DN 138:132162

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008615	A2	20030130	WO 2002-EP7375	20020703 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
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CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
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NE, SN, TD, TG
DE 10135053 A1 20030206 DE 2001-10135053 20010718

L161 ANSWER 5 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing genes sucA and sucB for the fermentative production of threonine
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76952 HCAPLUS
DN 138:132161

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 2003008614	A2	20030130	WO 2002-EP7374	20020703	<--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG
DE 10135053 A1 20030206 DE 2001-10135053 20010718

L161 ANSWER 6 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene sodA for the fermentative production of threonine
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76951 HCAPLUS
DN 138:132160

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 2003008613	A2	20030130	WO 2002-EP7373	20020703	<--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG
DE 10135053 A1 20030206 DE 2001-10135053 20010718

L161 ANSWER 7 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing genes rseA or rseC for the fermentative production of threonine
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
IN Rieping, Mechthild

AN 2003:76950 HCAPLUS
DN 138:132159

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008612	A2	20030130	WO 2002-EP7370	20020703 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10135053	A1	20030206	DE 2001-10135053	20010718

L161 ANSWER 8 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene talB for the fermentative production of threonine
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76949 HCAPLUS
DN 138:132158

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008611	A2	20030130	WO 2002-EP7369	20020703 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10135053	A1	20030206	DE 2001-10135053	20010718

L161 ANSWER 9 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene pfkB for the fermentative production of threonine
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76948 HCAPLUS
DN 138:132157

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008610	A2	20030130	WO 2002-EP7368	20020703 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

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DE 10135053 A1 20030206 DE 2001-10135053 20010718

L161 ANSWER 10 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene pykF for the fermentative production of threonine
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76947 HCAPLUS
DN 138:132156

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008609	A2	20030130	WO 2002-EP7367	20020703 <--

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DE 10135053 A1 20030206 DE 2001-10135053 20010718

L161 ANSWER 11 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene phoE for the fermentative production of threonine
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76946 HCAPLUS
DN 138:132155

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008608	A2	20030130	WO 2002-EP7366	20020703 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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DE 10135053 A1 20030206 DE 2001-10135053 20010718

L161 ANSWER 12 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli for the fermentative production of threonine
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76945 HCAPLUS
DN 138:118453

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008607	A2	20030130	WO 2002-EP7356	20020703 <--

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UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG
DE 10135053 A1 20030206 DE 2001-10135053 20010718

L161 ANSWER 13 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing genes phoB and phoR for the fermentative production of threonine
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76944 HCAPLUS
DN 138:132154

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 2003008606	A2	20030130	WO 2002-EP7355	20020703	<--

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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
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PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
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CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG
DE 10135053 A1 20030206 DE 2001-10135053 20010718

L161 ANSWER 14 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene malE for the fermentative production of threonine
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:76943 HCAPLUS
DN 138:132153

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 2003008605	A2	20030130	WO 2002-EP7354	20020703	<--

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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
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PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
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CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG
DE 10135053 A1 20030206 DE 2001-10135053 20010718

L161 ANSWER 15 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli for the fermentative production of threonine containing an attenuated aceB gene
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
IN Hermann, Thomas

AN 2003:76942 HCAPLUS
DN 138:132152

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008604	A2	20030130	WO 2002-EP7352	20020703 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10135051	A1	20030206	DE 2001-10135051	20010718

L161 ANSWER 16 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli for the fermentative production of threonine containing an attenuated aspA gene
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
IN Hermann, Thomas
AN 2003:76941 HCAPLUS
DN 138:132151

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008603	A2	20030130	WO 2002-EP7351	20020703 <--

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10135051	A1	20030206	DE 2001-10135051	20010718

L161 ANSWER 17 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli for the fermentative production of threonine containing an attenuated ugpB gene
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
IN Hermann, Thomas
AN 2003:76940 HCAPLUS
DN 138:132150

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003008602	A2	20030130	WO 2002-EP7350	20020703 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10135051 A1 20030206 DE 2001-10135051 20010718

L161 ANSWER 18 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing genes of the cysteine biosynthesis pathway for the fermentative production of threonine
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
IN Siebelt, Nicole; Widawka, Petra; Farwick, Mike
AN 2003:58256 HCAPLUS
DN 138:118448

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003006666	A2	20030123	WO 2002-EP6187	20020606 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10133667 A1 20030130 DE 2001-10133667 20010711

L161 ANSWER 19 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene dps for the fermentative production of threonine
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:42431 HCAPLUS
DN 138:84490

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003004675	A2	20030116	WO 2002-EP6568	20020614 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10132946 A1 20030116 DE 2001-10132946 20010706

L161 ANSWER 20 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing genes crr, ptsH, and ptsI for the fermentative production of threonine
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:42430 HCAPLUS
DN 138:84489

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003004674	A2	20030116	WO 2002-EP6562	20020614 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

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TJ, TM
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CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
DE 10132946 A1 20030116 DE 2001-10132946 20010706

L161 ANSWER 21 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene hns for the fermentative production of threonine
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:42427 HCAPLUS
DN 138:101972

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 2003004671	A2	20030116	WO 2002-EP6567	20020614	<--

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BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
DE 10132946 A1 20030116 DE 2001-10132946 20010706

L161 ANSWER 22 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene ptsG for the fermentative production of threonine
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:42426 HCAPLUS
DN 138:84488

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 2003004670	A2	20030116	WO 2002-EP6563	20020614	<--

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DE 10132946 A1 20030116 DE 2001-10132946 20010706

L161 ANSWER 23 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene mopB for the fermentative production of threonine
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:42425 HCAPLUS
DN 138:84487

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 2003004669	A2	20030116	WO 2002-EP6561	20020614	<--

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DE 10132946 A1 20030116 DE 2001-10132946 20010706

L161 ANSWER 24 OF 32 HCAPLUS COPYRIGHT 2003 ACS

TI Genetically modified Escherichia coli overexpressing gene lrp for the fermentative production of threonine

SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2

IN Rieping, Mechthild

AN 2003:42422 HCAPLUS

DN 138:84486

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2003004665	A2	20030116	WO 2002-EP6566	20020614	<--

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DE 10132946 A1 20030116 DE 2001-10132946 20010706

L161 ANSWER 25 OF 32 HCAPLUS COPYRIGHT 2003 ACS

TI Genetically modified Escherichia coli overexpressing gene fba for the fermentative production of threonine

SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2

IN Rieping, Mechthild

AN 2003:42421 HCAPLUS

DN 138:84485

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WO 2003004664	A2	20030116	WO 2002-EP6564	20020614	<--

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DE 10132946 A1 20030116 DE 2001-10132946 20010706

L161 ANSWER 26 OF 32 HCAPLUS COPYRIGHT 2003 ACS

TI Genetically modified Escherichia coli overexpressing genes ahpC and ahpF for the fermentative production of threonine

SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2

IN Rieping, Mechthild

AN 2003:42420 HCAPLUS
DN 138:84484

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003004663	A2	20030116	WO 2002-EP6560	20020614 <--

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DE 10132946	A1	20030116	DE 2001-10132946	20010706

L161 ANSWER 27 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli strains for the fermentative production of threonine
SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2
IN Hermann, Thomas
AN 2003:42419 HCAPLUS
DN 138:84483

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003004662	A2	20030116	WO 2002-EP5169	20020510 <--

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DE 10132945	A1	20030116	DE 2001-10132945	20010706
US 2003017556	A1	20030123	US 2002-186999	20020703

L161 ANSWER 28 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Genetically modified Escherichia coli overexpressing gene pgm for the fermentative production of threonine
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
IN Rieping, Mechthild
AN 2003:42360 HCAPLUS
DN 138:84481

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003004598	A2	20030116	WO 2002-EP6565	20020614 <--

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DE 10132946	A1	20030116	DE 2001-10132946	20010706

L161 ANSWER 29 OF 32 HCAPLUS COPYRIGHT 2003 ACS

TI Sequences of ppsA gene from corynebacteria and use thereof in production of L-lysine
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
IN Moeckel, Bettina; Marx, Achim; Bastuck, Christine; Buchholz, Michael; Pfefferle, Walter
AN 2002:220797 HCAPLUS
DN 136:261908

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002022829	A2	20020321	WO 2001-EP9456	20010816 <--
WO 2002022829	A3	20020711		
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DE 10045497	A1	20020328	DE 2000-10045497	20000913
AU 2002014949	A5	20020326	AU 2002-14949	20010816
EP 1317550	A2	20030611	EP 2001-983438	20010816
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002045224	A1	20020418	US 2001-946141	20010905

L161 ANSWER 30 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Recombinant Enterobacteriaceae overexpressing malate:quinone oxidoreductase gene mqo and their use in threonine production
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
IN Rieping, Mechthild; Thierbach, Georg; Van Der Rest, Michel Eduard; Molenaar, Douwe
AN 2002:72263 HCAPLUS
DN 136:133691

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002006459	A1	20020124	WO 2001-EP5548	20010516 <--
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DE 10103874	A1	20020131	DE 2001-10103874	20010130
US 2002127678	A1	20020912	US 2001-801042	20010308
EP 1303590	A1	20030423	EP 2001-943376	20010516
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

L161 ANSWER 31 OF 32 HCAPLUS COPYRIGHT 2003 ACS
TI Fermentative production of L-amino acids with poxB mutants of Enterobacteriaceae
SO Ger. Offen., 22 pp.
CODEN: GWXXBX
IN Thierbach, Georg; Rieping, Mechthild
AN 2002:349112 HCAPLUS
DN 136:354249

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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PI   DE 10112107       A1   20020508       DE 2001-10112107 20010314
     WO 2002036797     A2   20020510       WO 2001-EP11228  20010928 <--
     WO 2002036797     A3   20021114
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             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2002015910     A5   20020515       AU 2002-15910    20010928
     US 2003017554     A1   20030123       US 2002-76416    20020219

L161  ANSWER 32 OF 32  BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
TI    Engineering metabolic control, e.g. using promoters in specific host
      cells to optimize protein expression for either protein production or
      metabolite synthesis;
         lycopene and isoprenoid production by metabolic engineering of
         Escherichia coli
AU    Liao J C
AN    2001-06913  BIOTECHDS
PI    WO 2001007567 1 Feb 2001


=> fil .bec
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
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FULL ESTIMATED COST                                      58.38      73.86

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 13:41:40 ON 18 JUN 2003
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11 FILES IN THE FILE LIST

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FILE 'MEDLINE'
          9357 ISOPREN?
          1131 LYCOPENE#
         12510 CAROTEN?
L162     21806 ISOPREN? OR LYCOPENE# OR CAROTEN?

FILE 'SCISEARCH'
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L163     29214 ISOPREN? OR LYCOPENE# OR CAROTEN?

FILE 'LIFESCI'
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          3206 CAROTEN?
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FILE 'BIOTECHDS'
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FILE 'NTIS'
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L174         0 L162 AND L108

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L175         0 L163 AND L108

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L178          0 L166 AND L108

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L182          0 L170 AND L108

FILE 'BIOTECHNO'
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L183          0 L171 AND L108

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L184          1 L172 AND L108

TOTAL FOR ALL FILES
L185          4 L173 AND L108

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L186         2 L162 AND L84

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L188         1 L164 AND L84

FILE 'BIOTECHDS'
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          4448 SYNTHASE#
            21 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L189         0 L165 AND L84

FILE 'BIOSIS'
          1096 PPS
          3651 PHOSPHOENOL
         34782 PYRUVATE
         78919 SYNTHASE#
            11 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L190         3 L166 AND L84

FILE 'EMBASE'
          1381 PPS
           173 "PHOSPHOENOL"
         19215 "PYRUVATE"
         69481 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
                 ("PHOSPHOENOL"(W)"PYRUVATE"(W)SYNTHASE#)
L191         5 L167 AND L84

FILE 'HCAPLUS'
          2657 PPS
           676 PHOSPHOENOL
         46733 PYRUVATE
         72350 SYNTHASE#
             7 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L192         7 L168 AND L84

FILE 'NTIS'
           689 PPS
             5 PHOSPHOENOL
```

```
            304 PYRUVATE
            202 SYNTHASE#
              0 PHOSPHOENOL PYRUVATE SYNTHASE#
                  (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L193          0 L169 AND L84

FILE 'ESBIOBASE'
            419 PPS
             72 PHOSPHOENOL
           5427 PYRUVATE
          31769 SYNTHASE#
              0 PHOSPHOENOL PYRUVATE SYNTHASE#
                  (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L194          0 L170 AND L84

FILE 'BIOTECHNO'
            231 PPS
             77 PHOSPHOENOL
           6261 PYRUVATE
          27132 SYNTHASE#
              0 PHOSPHOENOL PYRUVATE SYNTHASE#
                  (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L195          1 L171 AND L84

FILE 'WPIDS'
           1273 PPS
            166 PHOSPHOENOL
           1620 PYRUVATE
           3209 SYNTHASE#
             24 PHOSPHOENOL PYRUVATE SYNTHASE#
                  (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L196          1 L172 AND L84

TOTAL FOR ALL FILES
L197         24 L173 AND L84

=> s l173 and (l24 not ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE))
FILE 'MEDLINE'
         37029 ACETYL
        123607 PHOSPHATE
           324 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
            71 ACETYLPHOSPHATE
         86014 ACETATE
         31039 PHORBOL
         26731 TETRADECANOYLPHORBOL
         86014 ACETATE
         30444 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L198       355 L162 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
                ))

FILE 'SCISEARCH'
         36635 ACETYL
        127161 PHOSPHATE
           311 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
            34 ACETYLPHOSPHATE
         83662 ACETATE
         29522 PHORBOL
          4491 TETRADECANOYLPHORBOL
         83662 ACETATE
         11169 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L199       563 L163 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
                ))
```

```
FILE 'LIFESCI'
         10624 "ACETYL"
         36365 "PHOSPHATE"
           166 ACETYL PHOSPHATE
                 ("ACETYL"(W)"PHOSPHATE")
            22 ACETYLPHOSPHATE
         23165 ACETATE
         11370 PHORBOL
          2294 TETRADECANOYLPHORBOL
         23165 ACETATE
          5584 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L200       118 L164 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
               ))

FILE 'BIOTECHDS'
          2604 ACETYL
         15692 PHOSPHATE
            48 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
            11 ACETYLPHOSPHATE
         11055 ACETATE
           274 PHORBOL
            47 TETRADECANOYLPHORBOL
         11055 ACETATE
           149 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L201        77 L165 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
               ))

FILE 'BIOSIS'
          83598 ACETYL
         186290 PHOSPHATE
            422 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             78 ACETYLPHOSPHATE
         112682 ACETATE
          37478 PHORBOL
           9328 TETRADECANOYLPHORBOL
         112682 ACETATE
          21297 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L202        677 L166 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
               ))

FILE 'EMBASE'
          38373 "ACETYL"
         151764 "PHOSPHATE"
            265 ACETYL PHOSPHATE
                  ("ACETYL"(W)"PHOSPHATE")
             40 ACETYLPHOSPHATE
          99814 ACETATE
          36797 PHORBOL
           5982 TETRADECANOYLPHORBOL
          99814 ACETATE
          24891 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L203        766 L167 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
               ))

FILE 'HCAPLUS'
         133044 ACETYL
         482932 PHOSPHATE
            925 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
            236 ACETYLPHOSPHATE
         449484 ACETATE
```

```
         30933 PHORBOL
          6319 TETRADECANOYLPHORBOL
        449484 ACETATE
         15768 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L204      4128 L168 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
               ))

FILE 'NTIS'
           725 ACETYL
          6281 PHOSPHATE
             1 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
             1 ACETYLPHOSPHATE
          3039 ACETATE
           194 PHORBOL
            29 TETRADECANOYLPHORBOL
          3039 ACETATE
            80 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L205         7 L169 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
               ))

FILE 'ESBIOBASE'
         11210 ACETYL
         35348 PHOSPHATE
           135 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
            16 ACETYLPHOSPHATE
         22040 ACETATE
         10955 PHORBOL
          1968 TETRADECANOYLPHORBOL
         22040 ACETATE
          4576 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L206       191 L170 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
               ))

FILE 'BIOTECHNO'
         11762 ACETYL
         48786 PHOSPHATE
           184 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
            28 ACETYLPHOSPHATE
         28164 ACETATE
         18056 PHORBOL
          3163 TETRADECANOYLPHORBOL
         28164 ACETATE
         11969 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L207       161 L171 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
               ))

FILE 'WPIDS'
         23959 ACETYL
         79708 PHOSPHATE
            31 ACETYL PHOSPHATE
                 (ACETYL(W)PHOSPHATE)
            17 ACETYLPHOSPHATE
        109139 ACETATE
           288 PHORBOL
            40 TETRADECANOYLPHORBOL
        109139 ACETATE
           137 (PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
L208      1569 L172 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
               ))

TOTAL FOR ALL FILES
```

```
L209        8612 L173 AND (L24 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE
                 ))

=> s l173(5a)(synthes? or production# or mak?)
FILE 'MEDLINE'
          427413 SYNTHES?
          305768 PRODUCTION#
          247920 MAK?
L210         846 L162(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'SCISEARCH'
          739600 SYNTHES?
          479606 PRODUCTION#
          266667 MAK?
L211        1635 L163(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'LIFESCI'
          126867 SYNTHES?
          161711 PRODUCTION#
           45002 MAK?
L212         533 L164(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'BIOTECHDS'
           25939 SYNTHES?
          107549 PRODUCTION#
            8620 MAK?
L213         404 L165(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'BIOSIS'
          584576 SYNTHES?
          543711 PRODUCTION#
          163135 MAK?
L214        2178 L166(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'EMBASE'
          523551 SYNTHES?
          316131 PRODUCTION#
          213006 MAK?
L215         772 L167(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'HCAPLUS'
         1296882 SYNTHES?
          493972 PRODUCTION#
          759068 PRODN
         1053236 PRODUCTION#
                   (PRODUCTION# OR PRODN)
          495793 MAK?
L216        4967 L168(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'NTIS'
           41089 SYNTHES?
          129891 PRODUCTION#
          114971 MAK?
L217          21 L169(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'ESBIOBASE'
          148053 SYNTHES?
          150320 PRODUCTION#
           50602 MAK?
L218         562 L170(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'BIOTECHNO'
          162184 SYNTHES?
          140843 PRODUCTION#
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         32178 MAK?
L219       468 L171(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

FILE 'WPIDS'
        106127 SYNTHES?
        298074 PRODUCTION#
        473786 PRODN
        753376 PRODUCTION#
                 (PRODUCTION# OR PRODN)
        558784 MAK?
L220      1019 L172(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

TOTAL FOR ALL FILES
L221     13405 L173(5A)(SYNTHES? OR PRODUCTION# OR MAK?)

=> s l209 and l221
FILE 'MEDLINE'
L222        35 L198 AND L210

FILE 'SCISEARCH'
L223        42 L199 AND L211

FILE 'LIFESCI'
L224        17 L200 AND L212

FILE 'BIOTECHDS'
L225         9 L201 AND L213

FILE 'BIOSIS'
L226        72 L202 AND L214

FILE 'EMBASE'
L227        32 L203 AND L215

FILE 'HCAPLUS'
L228       280 L204 AND L216

FILE 'NTIS'
L229         2 L205 AND L217

FILE 'ESBIOBASE'
L230        22 L206 AND L218

FILE 'BIOTECHNO'
L231        15 L207 AND L219

FILE 'WPIDS'
L232        45 L208 AND L220

TOTAL FOR ALL FILES
L233       571 L209 AND L221

=> s (l185 or l197 or l233) not 2001-2003/py
FILE 'MEDLINE'
       1261926 2001-2003/PY
L234        35 (L174 OR L186 OR L222) NOT 2001-2003/PY

FILE 'SCISEARCH'
       2305749 2001-2003/PY
L235        43 (L175 OR L187 OR L223) NOT 2001-2003/PY

FILE 'LIFESCI'
        223576 2001-2003/PY
L236        17 (L176 OR L188 OR L224) NOT 2001-2003/PY
```

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FILE 'BIOTECHDS'
         46337 2001-2003/PY
L237          5 (L177 OR L189 OR L225) NOT 2001-2003/PY

FILE 'BIOSIS'
       1215331 2001-2003/PY
L238         70 (L178 OR L190 OR L226) NOT 2001-2003/PY

FILE 'EMBASE'
       1044608 2001-2003/PY
L239         34 (L179 OR L191 OR L227) NOT 2001-2003/PY

FILE 'HCAPLUS'
       2421784 2001-2003/PY
L240        255 (L180 OR L192 OR L228) NOT 2001-2003/PY

FILE 'NTIS'
         33435 2001-2003/PY
L241          1 (L181 OR L193 OR L229) NOT 2001-2003/PY

FILE 'ESBIOBASE'
        671253 2001-2003/PY
L242         19 (L182 OR L194 OR L230) NOT 2001-2003/PY

FILE 'BIOTECHNO'
        271276 2001-2003/PY
L243         14 (L183 OR L195 OR L231) NOT 2001-2003/PY

FILE 'WPIDS'
       2253073 2001-2003/PY
L244         28 (L184 OR L196 OR L232) NOT 2001-2003/PY

TOTAL FOR ALL FILES
L245        521 (L185 OR L197 OR L233) NOT 2001-2003/PY

=> dup rem l245
PROCESSING COMPLETED FOR L245
L246         324 DUP REM L245 (197 DUPLICATES REMOVED)

=> d tot

L246  ANSWER 1 OF 324  BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
TI    Manufacture of actinol useful for synthesizing
      carotenoids by selective asymmetric reduction of levodione with
      new Cellulomonas, Corynebacterium, Planococcus and Arthrobacter
      microorganisms;
         production of actinol by reacting Cellulomonas species,
         Corynebacterium aquaticum, Planococcus akeanokoites or Arthrobacter
         sulfureus with levodione
AU    Shimizu S; Wada M
AN    2000-06238  BIOTECHDS
PI    EP 982406 1 Mar 2000

L246 ANSWER 2 OF 324  HCAPLUS  COPYRIGHT 2003 ACS
TI   The use of cholesterol-synthesis inhibitors for the reduction of the level
     of cholesterol in poultry eggs
SO   Eur. Pat. Appl., 19 pp.
     CODEN: EPXXDW
IN   Kramer, Klaus; Baldenius, Kai-Uwe; Hoppe, Peter Paul
AN   2000:98040  HCAPLUS
DN   132:136828
     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ----------------  ----  --------      ---------------  --------
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PI EP 978236 A1 20000209 EP 1999-115698 19990809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
DE 19835850 A1 20000210 DE 1998-19835850 19980807
US 6166067 A 20001226 US 1999-362062 19990728
JP 2000060435 A2 20000229 JP 1999-221602 19990804
CN 1258457 A 20000705 CN 1999-119696 19990807

L246 ANSWER 3 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 1
TI Effect of the solvent environment on the spectroscopic properties and dynamics of the lowest excited states of **carotenoids**
SO JOURNAL OF PHYSICAL CHEMISTRY B, (11 MAY 2000) Vol. 104, No. 18, pp. 4569-4577.
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
ISSN: 1089-5647.
AU Frank H A (Reprint); Bautista J A; Josue J; Pendon Z; Hiller R G; Sharples F P; Gosztola D; Wasielewski M R
AN 2000:376281 SCISEARCH

L246 ANSWER 4 OF 324 MEDLINE DUPLICATE 2
TI Antioxidant activity of dietary polyphenols as determined by a modified ferric reducing/antioxidant power assay.
SO JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, (2000 Aug) 48 (8) 3396-402.
Journal code: 0374755. ISSN: 0021-8561.
AU Pulido R; Bravo L; Saura-Calixto F
AN 2000458862 MEDLINE

L246 ANSWER 5 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Design and Synthesis of a Transferable Farnesyl Pyrophosphate Analogue to Ras by Protein Farnesyltransferase
SO Journal of Organic Chemistry (2000), 65(10), 3027-3033
CODEN: JOCEAH; ISSN: 0022-3263
AU Chehade, Kareem A. H.; Andres, Douglas A.; Morimoto, Hiromi; Spielmann, H. Peter
AN 2000:239015 HCAPLUS
DN 133:17642

L246 ANSWER 6 OF 324 MEDLINE DUPLICATE 3
TI Changes in **isoprenoid** lipid **synthesis** by gemfibrozil and clofibric acid in rat hepatocytes.
SO BIOCHEMICAL PHARMACOLOGY, (2000 May 15) 59 (10) 1203-10.
Journal code: 0101032. ISSN: 0006-2952.
AU Hashimoto F; Taira S; Hayashi H
AN 2000202023 MEDLINE

L246 ANSWER 7 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Forskolin studies
SO Tetrahedron (2000), 56(8), 1081-1095
CODEN: TETRAB; ISSN: 0040-4020
AU Behnke, Dirk; Hennig, Lothar; Findeisen, Matthias; Welzel, Peter; Muller, Dietrich; Thormann, Michael; Hofmann, Hans-Jorg
AN 2000:147117 HCAPLUS
DN 132:279368

L246 ANSWER 8 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 4
TI Biosynthesis of **carotenoids** in the chloroplasts of algae and higher plants
SO RUSSIAN JOURNAL OF PLANT PHYSIOLOGY, (NOV-DEC 2000) Vol. 47, No. 6, pp. 796-814.
Publisher: MAIK NAUKA/INTERPERIODICA, C/O KLUWER ACADEMIC-PLENUM PUBLISHERS, 233 SPRING ST, NEW YORK, NY 10013-1578.
ISSN: 1021-4437.
AU Ladygin V G (Reprint)
AN 2000:904268 SCISEARCH

L246 ANSWER 9 OF 324 MEDLINE DUPLICATE 5
TI Metabolism of farnesyl diphosphate in tobacco BY-2 cells treated with squalestatin.
SO BIOCHEMICAL SOCIETY TRANSACTIONS, (2000 Dec) 28 (6) 794-6.
Journal code: 7506897. ISSN: 0300-5127.
AU Hartmann M A; Wentzinger L; Hemmerlin A; Bach T J
AN 2001301221 MEDLINE

L246 ANSWER 10 OF 324 MEDLINE DUPLICATE 6
TI Improving **lycopene production** in Escherichia coli by engineering metabolic control.
SO NATURE BIOTECHNOLOGY, (2000 May) 18 (5) 533-7.
Journal code: 9604648. ISSN: 1087-0156.
AU Farmer W R; Liao J C
AN 2000264176 MEDLINE

L246 ANSWER 11 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Ethylene and glycosidase promotion in GA3- and IAA-treated tomato fruit (Lycopersicon esculentum Mill.)
SO Journal of Plant Growth Regulation (2000), 19(3), 359-368
CODEN: JPGRDI; ISSN: 0721-7595
AU Sozzi, G. O.; Trinchero, G. D.; Fraschina, A. A.
AN 2001:286480 HCAPLUS
DN 135:43583

L246 ANSWER 12 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 7
TI Emission of volatiles from brown boronia flowers: Some comparative observations
SO ANNALS OF BOTANY, (AUG 2000) Vol. 86, No. 2, pp. 347-354.
Publisher: ACADEMIC PRESS LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.
ISSN: 0305-7364.
AU MacTavish H S (Reprint); Davies N W; Menary R C
AN 2000:596461 SCISEARCH

L246 ANSWER 13 OF 324 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Protein phosphatase activity is increased in a rat model of long-term .beta.-adrenergic stimulation.
SO Naunyn-Schmiedeberg's Archives of Pharmacology, (2000) 362/3 (222-231).
Refs: 60
ISSN: 0028-1298 CODEN: NSAPCC
AU Boknik P.; Fockenbrock M.; Herzig S.; Knapp J.; Linck B.; Luss H.; Muller F.U.; Muller T.; Schmitz W.; Schroder F.; Neumann J.
AN 2000316049 EMBASE

L246 ANSWER 14 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 8
TI Fosmidomycin as an inhibitor of the non-mevalonate terpenoid pathway depresses **synthesis** of secondary **carotenoids** in flagellates of the green alga Haematococcus pluvialis
SO JOURNAL OF APPLIED BOTANY-ANGEWANDTE BOTANIK, (SEP 2000) Vol. 74, No. 3-4, pp. 137-140.
Publisher: BLACKWELL WISSENSCHAFTS-VERLAG GMBH, KURFURSTENDAMM 57, D-10707 BERLIN, GERMANY.
ISSN: 0949-5460.
AU Hagen C (Reprint); Grunewald K
AN 2000:716267 SCISEARCH

L246 ANSWER 15 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Roseinatronobacter thiooxidans gen. nov., sp. nov., a new alkaliphilic aerobic bacteriochlorophyll a-containing bacterium isolated from a soda lake.
SO Mikrobiologiya, (Jan. Feb., 2000) Vol. 69, No. 1, pp. 89-97. print.
ISSN: 0026-3656.
AU Sorokin, D. Yu. (1); Tourova, T. P.; Kuznetsov, B. B.; Bryantseva, I. A.;

Gorlenko, V. M.
AN 2000:384119 BIOSIS

L246 ANSWER 16 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 9
TI Roseinatronobacter thiooxidans gen. nov., sp, nov., a new alkaliphilic aerobic bacteriochlorophyll a - containing bacterium isolated from a soda lake
SO MICROBIOLOGY, (JAN-FEB 2000) Vol. 69, No. 1, pp. 75-82.
Publisher: MAIK NAUKA/INTERPERIODICA, C/O PLENUM/CONSULTANTS BUREAU 233 SPRING ST, NEW YORK, NY 10013.
ISSN: 0026-2617.
AU Sorokin D Y (Reprint); Tourova T P; Kuznetsov B B; Bryantseva I A; Gorlenko V M
AN 2000:220386 SCISEARCH

L246 ANSWER 17 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 10
TI Separation of chlorophylls and **carotenoids** from marine phytoplankton: a new HPLC method using a reversed phase C-8 column and pyridine-containing mobile phases
SO MARINE ECOLOGY-PROGRESS SERIES, (APR 2000) Vol. 195, pp. 29-45.
Publisher: INTER-RESEARCH, NORDBUNTE 23, D-21385 OLDENDORF LUHE, GERMANY.
ISSN: 0171-8630.
AU Zapata M (Reprint); Rodriguez F; Garrido J L
AN 2000:340849 SCISEARCH

L246 ANSWER 18 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Application and synthesis of chloro(halo)isopentenyl **acetate**
SO Shanghai Huagong (2000), 25(6), 11-14
CODEN: SHAHE2; ISSN: 1004-017X
AU Chen, Yu; Xia, Shunwei; Fu, Jiansong
AN 2000:319928 HCAPLUS
DN 133:176941

L246 ANSWER 19 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Process for **making** metabolites of **lycopene**.
SO Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 28, 1999) Vol. 1229, No. 4, pp. No pagination. e-file.
ISSN: 0098-1133.
AU Pfander, Hanspeter (1); Traber, Bruno
AN 2000:301644 BIOSIS

L246 ANSWER 20 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Production of paintable/bondable polymeric articles by treatment with oxidizing agents
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
IN Beholz, Lars Guenter
AN 1999:626234 HCAPLUS
DN 131:244247

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9948933	A1	19990930	WO 1999-US6270	19990324
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6077913	A	20000620	US 1998-48609	19980326
US 6100343	A	20000808	US 1998-196608	19981103
CA 2325732	AA	19990930	CA 1999-2325732	19990324
AU 9931981	A1	19991018	AU 1999-31981	19990324

L246 ANSWER 21 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Method for accelerated uptake of **carotenoid** mixtures into serum and tissues
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
IN Tronnier, Hagen
AN 1999:626018 HCAPLUS
DN 131:248057

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9948468	A1	19990930	WO 1999-EP1661	19990313
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19812777	A1	19991007	DE 1998-19812777	19980324

L246 ANSWER 22 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Regio- and stereoselective synthesis of N-H aziridines by N-N bond reduction of N-quinazolinyl aziridines
SO Tetrahedron (1999), 55(32), 9669-9686
CODEN: TETRAB; ISSN: 0040-4020
AU Koohang, Ali; Stanchina, Corey L.; Coates, Robert M.
AN 1999:512063 HCAPLUS
DN 131:271853

L246 ANSWER 23 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI Inhibition of trichothecin and ergosterol biosynthesis in Trichothecium roseum by lovastatin
SO JOURNAL OF THE CHINESE CHEMICAL SOCIETY, (OCT 1999) Vol. 46, No. 5, pp. 687-692.
Publisher: CHINESE CHEM SOC, PO BOX 609, TAIPEI 10099, TAIWAN.
ISSN: 0009-4536.
AU Huang W L; Lee K R; Shiao M S (Reprint)
AN 1999:807008 SCISEARCH

L246 ANSWER 24 OF 324 MEDLINE DUPLICATE 11
TI Enhancement of sterol synthesis by the monoterpene perillyl alcohol is unaffected by competitive 3-hydroxy-3-methylglutaryl-CoA reductase inhibition.
SO LIPIDS, (1999 Jun) 34 (6) 605-15.
Journal code: 0060450. ISSN: 0024-4201.
AU Cerda S R; Wilkinson J 4th; Branch S K; Broitman S A
AN 1999334447 MEDLINE

L246 ANSWER 25 OF 324 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 12
TI Integration of the metabolic pathways of steroids, **carotenoids**, and retinoids.
SO Critical Reviews in Biochemistry and Molecular Biology, (1999) 34/6 (405-410).
Refs: 31
ISSN: 1040-9238 CODEN: CRBBEJ
AU Gawienowski A.M.
AN 2000037032 EMBASE

L246 ANSWER 26 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 13
TI Atmospheric chemistry over the auyantepuy - (5 degrees 46' N; 62 degrees 32' W; 2100 meters asl)
SO INTERCIENCIA, (NOV-DEC 1999) Vol. 24, No. 6, pp. 372-380.
Publisher: INTERCIENCIA, APARTADO 51842, CARACAS 1050A, VENEZUELA.
ISSN: 0378-1844.
AU Sanhueza E (Reprint); Donoso L; Santana M; Fernandez E; Romero J
AN 2000:21195 SCISEARCH

L246 ANSWER 27 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI Production of wax esters during aerobic growth of marine bacteria on **isoprenoid** compounds
SO APPLIED AND ENVIRONMENTAL MICROBIOLOGY, (JAN 1999) Vol. 65, No. 1, pp. 221-230.
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0099-2240.
AU Rontani J F (Reprint); Bonin P C; Volkman J K
AN 1999:61012 SCISEARCH

L246 ANSWER 28 OF 324 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
TI Production of astaxanthin in Haematococcus pluvialis cultured in various media;
the effect of culture medium composition on **carotenoid production** by an alga, for use in the food industry
SO Bioresource Technol.; (1999) 68, 2, 197-99
CODEN: BIRTEB ISSN: 0960-8524
AU Tripathi U; Sarada R; Rao S R; *Ravishankar G A
AN 1999-04914 BIOTECHDS

L246 ANSWER 29 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI New plasticizer EDOS for polar polymers on base of formals of dioxane alcohols
SO Scientific Israel--Technological Advantages (1999), 1(1), 8-15
CODEN: SITAFG
AU Gotlib, E. M.; Grinberg, L. P.; Verizhnikov, L. V.; Liakumovich, A. G.
AN 1999:415543 HCAPLUS
DN 131:215105

L246 ANSWER 30 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Production method of adhesive tape with good adhesion
SO Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
IN Tokuda, Kenji; Matsuki, Chikara; Shimizu, Ikusuke
AN 1998:334829 HCAPLUS
DN 129:42028

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 10140112	A2	19980526	JP 1996-304592	19961115

L246 ANSWER 31 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Preparation of retinyl triphenylphosphonium salts.
PI RU 2119494 C1 19980927 (200015)* C07F009-54
IN BELOVA, V M; BELOVODSKII, V P; OZOROVA, T I

L246 ANSWER 32 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 15
TI 2,6-cyclolycopene-1,5-diol: Total synthesis of a naturally occurring oxidation product of **lycopene**
SO TETRAHEDRON, (30 JUL 1998) Vol. 54, No. 31, pp. 9011-9022.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
ISSN: 0040-4020.
AU Traber B; Pfander H (Reprint)
AN 1998:551305 SCISEARCH

L246 ANSWER 33 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The 1-deoxy-D-xylulose-5-phosphate pathway for biosynthesis of **carotenoids** and other plastidic **isoprenoids**
SO Photosynthesis: Mechanisms and Effects, Proceedings of the International Congress on Photosynthesis, 11th, Budapest, Aug. 17-22, 1998 (1998), Volume 4, 3215-3220. Editor(s): Garab, Gyozo. Publisher: Kluwer Academic Publishers, Dordrecht, Neth.
CODEN: 68VVAS

AU Lichtenthaler, Hartmut K.; Schwender, Jorg; Muller, Christian
AN 2000:284717 HCAPLUS
DN 133:319495

L246 ANSWER 34 OF 324 MEDLINE DUPLICATE 16
TI Cloning and characterization of a gene from Escherichia coli encoding a transketolase-like enzyme that catalyzes the synthesis of D-1-deoxyxylulose 5-phosphate, a common precursor for **isoprenoid**, thiamin, and pyridoxol biosynthesis.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Mar 3) 95 (5) 2105-10.
Journal code: 7505876. ISSN: 0027-8424.
AU Lois L M; Campos N; Putra S R; Danielsen K; Rohmer M; Boronat A
AN 1998151473 MEDLINE

L246 ANSWER 35 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI A family of transketolases that directs **isoprenoid** biosynthesis via a mevalonate-independent pathway
SO Proceedings of the National Academy of Sciences of the United States of America (1998), 95(5), 2100-2104
CODEN: PNASA6; ISSN: 0027-8424
AU Lange, B. Markus; Wildung, Mark R.; McCaskill, David; Croteau, Rodney
AN 1998:173074 HCAPLUS
DN 128:305603

L246 ANSWER 36 OF 324 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
TI Biological activities of abscisic acid analogs in the morphological change of the green alga Haematococcus pluvialis; for e.g. astaxanthin production
SO J.Ferment.Bioeng.; (1998) 85, 5, 529-31
CODEN: JFBIEX ISSN: 0922-338X
AU Kobayashi M; Todoroki Y; Hirai N; Kurimura Y; Ohigashi H; Tsuji Y
AN 1998-10565 BIOTECHDS

L246 ANSWER 37 OF 324 MEDLINE DUPLICATE 17
TI Distribution of the mevalonate and glyceraldehyde phosphate/pyruvate pathways for **isoprenoid** biosynthesis in unicellular algae and the cyanobacterium Synechocystis PCC 6714.
SO BIOCHEMICAL JOURNAL, (1998 Jul 15) 333 (Pt 2) 381-8.
Journal code: 2984726R. ISSN: 0264-6021.
AU Disch A; Schwender J; Muller C; Lichtenthaler H K; Rohmer M
AN 1998324900 MEDLINE

L246 ANSWER 38 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI On the absence of the glyceraldehyde 3-phosphate/pyruvate pathway for **isoprenoid** biosynthesis in fungi and yeasts.
SO FEMS Microbiology Letters, (Nov. 15, 1998) Vol. 168, No. 2, pp. 201-208.
ISSN: 0378-1097.
AU Disch, Andrea; Rohmer, Michel (1)
AN 1999:5130 BIOSIS

L246 ANSWER 39 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Production of astaxanthin in Haematococcus pluvialis cultured in various media
SO Bioresource Technology (1998), Volume Date 1999, 68(2), 197-199
CODEN: BIRTEB; ISSN: 0960-8524
AU Tripathi, Usha; Sarada, R.; Rao, S. Ramachandra; Ravishankar, G. A.
AN 1999:115935 HCAPLUS
DN 130:222206

L246 ANSWER 40 OF 324 MEDLINE DUPLICATE 18
TI Distribution of mevalonate and glyceraldehyde 3-phosphate/pyruvate routes for **isoprenoid** biosynthesis in some gram-negative bacteria and mycobacteria.

SO FEMS MICROBIOLOGY LETTERS, (1998 Jul 1) 164 (1) 169-75.
Journal code: 7705721. ISSN: 0378-1097.
AU Putra S R; Disch A; Bravo J M; Rohmer M
AN 1998340514 MEDLINE

L246 ANSWER 41 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Study on **production** conditions of **carotenoid**
SO Shipin Kexue (Beijing) (1998), 19(8), 20-22
CODEN: SPKHD5; ISSN: 1002-6630
AU Yang, Ge; Li, Ya
AN 1998:761146 HCAPLUS
DN 130:181535

L246 ANSWER 42 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 19
TI Inhibition of plant growth by mevinolin and reversal of this inhibition by **isoprenoids**
SO SOUTH AFRICAN JOURNAL OF BOTANY, (FEB 1998) Vol. 64, No. 1, pp. 18-24.
Publisher: BUREAU SCIENTIFIC PUBL, P O BOX 2600, PRETORIA 0001, SOUTH AFRICA.
ISSN: 0254-6299.
AU Josekutty P C (Reprint)
AN 1998:304704 SCISEARCH

L246 ANSWER 43 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Glue composition for footwear **production** - comprises butadiene-nitrile rubber, chlorinated **isoprene**, tert-butyl-phenol formaldehyde resin, zinc and magnesium oxide(s), silica, and ethyl **acetate**.
PI RU 2078108 C1 19970427 (199805)* 7p C09J109-02
IN GLAGOLEV, V A; LYUSOVA, L R; NORKIN, I S

L246 ANSWER 44 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Total synthesis of C31-methyl ketone apocarotenoids 3. On the structure of hopkinsiaxanthin: first total synthesis of (all-E)-(3S)- and (9Z)-(3S)-7'-apohopkinsiaxanthin
SO Acta Chemica Scandinavica (1997), 51(12), 1201-1216
CODEN: ACHSE7; ISSN: 0904-213X
AU Haugan, Jarle Andre; Lobkovsky, Emil; Liaaen-Jensen, Synnve
AN 1997:751755 HCAPLUS
DN 128:48384

L246 ANSWER 45 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Photobiology of the Gonyaulax circadian system. Part 2. Allopurinol inhibits blue-light effects
SO Planta (1997), 202(4), 502-509
CODEN: PLANAB; ISSN: 0032-0935
AU Deng, Tzu Shing; Roenneberg, Till
AN 1997:518058 HCAPLUS
DN 127:202708

L246 ANSWER 46 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 20
TI DIELS-ALDER REACTION OF IN-SITU GENERATED P-BENZOQUINONES WITH **ISOPRENOIDAL** DIENOL **ACETATE** - NOVEL **SYNTHESIS** OF 2-**ISOPRENOIDAL** NAPHTHALENE-5,8-QUINOLS
SO TETRAHEDRON LETTERS, (28 OCT 1996) Vol. 37, No. 44, pp. 8037-8040.
ISSN: 0040-4039.
AU RANI A; KUMAR B; SURYAWANSHI S N (Reprint); BHAKUNI D S
AN 96:814389 SCISEARCH

L246 ANSWER 47 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Micellization of Model Graft Copolymers of the H and .pi. Type in Dilute Solution
SO Macromolecules (1996), 29(23), 7378-7385
CODEN: MAMOBX; ISSN: 0024-9297

AU Pispas, Stergios; Hadjichristidis, Nikos; Mays, Jimmy W.
AN 1996:623246 HCAPLUS
DN 125:330151

L246 ANSWER 48 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 21
TI Protein kinase C in cultured human placental trophoblasts: Identification of isoforms and role in cAMP signalling
SO BIOCHEMICAL JOURNAL, (15 DEC 1996) Vol. 320, Part 3, pp. 831-836. Publisher: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON, ENGLAND W1N 3AJ. ISSN: 0264-6021.
AU Karl P I (Reprint); Divald A
AN 97:36672 SCISEARCH

L246 ANSWER 49 OF 324 MEDLINE DUPLICATE 22
TI Alterations in cell cholesterol content modulate Ca(2+)-induced tight junction assembly by MDCK cells.
SO LIPIDS, (1996 Aug) 31 (8) 817-28. Journal code: 0060450. ISSN: 0024-4201.
AU Stankewich M C; Francis S A; Vu Q U; Schneeberger E E; Lynch R D
AN 97023524 MEDLINE

L246 ANSWER 50 OF 324 MEDLINE DUPLICATE 23
TI Separate compartments for the **production** of sterols, **carotenoids** and gibberellins in Gibberella fujikuroi.
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1996 Aug 1) 239 (3) 720-5. Journal code: 0107600. ISSN: 0014-2956.
AU Domenech C E; Giordano W; Avalos J; Cerda-Olmedo E
AN 96370822 MEDLINE

L246 ANSWER 51 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Carbon sources for fatty acid and sterol biosynthesis in Leishmania species
SO Biochemical Society Transactions (1996), 24(3), 434S CODEN: BCSTB5; ISSN: 0300-5127
AU Ginger, Michael L.; Chance, Michael L.; Goad, L. John
AN 1996:570519 HCAPLUS
DN 125:296815

L246 ANSWER 52 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Example 8: .beta.,.beta.-**carotene**
SO Carotenoids (1996), Volume 2, 327-329. Editor(s): Britton, George; Liaaen-Jensen, Synnoeve; Pfander, Hanspeter. Publisher: Birkhaeuser, Boston, Mass. CODEN: 60YYAW
AU Paust, Joachim; Manchand, Percy S.
AN 1996:535238 HCAPLUS
DN 125:196054

L246 ANSWER 53 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoid synthesis**. Sulfone coupling
SO Carotenoids (1996), Volume 2, 311-314. Editor(s): Britton, George; Liaaen-Jensen, Synnoeve; Pfander, Hanspeter. Publisher: Birkhaeuser, Boston, Mass. CODEN: 60YYAW
AU Otera, Junzo
AN 1996:535234 HCAPLUS
DN 125:222184

L246 ANSWER 54 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Thermal and NMR characterization of polysulfones prepared from 1,3 dienes and olefins
SO Book of Abstracts, 211th ACS National Meeting, New Orleans, LA, March 24-28 (1996), POLY-174 Publisher: American Chemical Society, Washington, D. C.

CODEN: 62PIAJ
AU Davies, Jack D.; Daly, William H.
AN 1996:221909 HCAPLUS

L246 ANSWER 55 OF 324 MEDLINE DUPLICATE 24
TI Evidence for farnesol-mediated **isoprenoid synthesis** regulation in a halophilic archaeon, Haloferax volcanii.
SO FEBS LETTERS, (1996 Jan 22) 379 (1) 43-6.
Journal code: 0155157. ISSN: 0014-5793.
AU Tachibana A; Tanaka T; Taniguchi M; Oi S
AN 96159018 MEDLINE

L246 ANSWER 56 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Farnesyl compounds as cholesterol-lowering agents
SO U.S., 6 pp.
CODEN: USXXAM
IN Bradfute, David L.; Simoni, Robert D.
AN 1996:35008 HCAPLUS
DN 124:106678

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5475029	A	19951212	US 1993-88698	19930708

L246 ANSWER 57 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI **Prodn**. of beta **carotene** in improved yield - by condensing retinyl-tri phenyl-phosphonic acid salt.
PI RU 2032667 C1 19950410 (199610)* 4p C07C403-24
IN SAMOKUVALOV, G I; VAKULOVA, L A; ZHIDKOVA, T A

L246 ANSWER 58 OF 324 MEDLINE DUPLICATE 25
TI Ubiquinone biosynthesis in Leishmania major promastigotes.
SO INTERNATIONAL JOURNAL FOR PARASITOLOGY, (1995 Mar) 25 (3) 279-84.
Journal code: 0314024. ISSN: 0020-7519.
AU Ranganathan G; Mukkada A J
AN 95325056 MEDLINE

L246 ANSWER 59 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 26
TI C-15-ALLENIC MODEL COMPOUNDS FOR **CAROTENOIDS - SYNTHESIS** , COMPARATIVE H-1-NMR DATA AND A NEW INTRAMOLECULAR REACTION
SO ACTA CHEMICA SCANDINAVICA, (APR 1995) Vol. 49, No. 4, pp. 271-277.
ISSN: 0904-213X.
AU HAUGAN J A (Reprint); LIAAENJENSEN S
AN 95:311339 SCISEARCH

L246 ANSWER 60 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 27
TI ENVIRONMENTAL AND DEVELOPMENTAL REGULATION OF **CAROTENOGENESIS** IN THE DIMORPHIC FUNGUS MUCOR-ROUXII
SO CURRENT MICROBIOLOGY, (SEP 1995) Vol. 31, No. 3, pp. 141-145.
ISSN: 0343-8651.
AU MOSQUEDACANO G; GUTIERREZCORONA J F (Reprint)
AN 95:518533 SCISEARCH

L246 ANSWER 61 OF 324 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
TI Phaffia strains transformed with genes encoding heterologous protein or **carotenoid**;
Phaffia rhodozyma transformation; potential in recombinant protein and **carotenoid** e.g. astaxanthin, zeaxanthin, cantaxanthin and beta-**carotene production**
AN 1994-06988 BIOTECHDS
PI WO 9406918 31 Mar 1994

L246 ANSWER 62 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** of .beta.-**carotene**
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 10 pp.

CODEN: CNXXEV
IN Zheng, Qingquan
AN 1995:874825 HCAPLUS
DN 123:256440

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN 1090271	A	19940803	CN 1993-117490	19930920

L246 ANSWER 63 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Complex of biologically active lipids **prodn**. - with increase in **carotenoid** content by using a medium contg. sodium **acetate** and vitamin B1.
PI RU 2022019 C1 19941030 (199526)* 4p C12P007-64
IN FUNTIKOVA, N S; KONOVA, I V; TORLANOVA, B D

L246 ANSWER 64 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Palladium-catalyzed vinylation of tertiary allylic alcohols: a new protocol for the **synthesis** of **isoprenoid** aldehydes
SO Tetrahedron (1994), 50(11), 3389-96
CODEN: TETRAB; ISSN: 0040-4020
AU Bienayme, Hugues; Yezeguelian, Catherine
AN 1994:605716 HCAPLUS
DN 121:205716

L246 ANSWER 65 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of natural products
SO Hwahak Sekye (1994), 34(11), 1056-9
CODEN: HWSEEX; ISSN: 1225-004X
AU Shin, G. H.
AN 1995:556661 HCAPLUS
DN 123:51769

L246 ANSWER 66 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** of isotopically labeled **carotenoids**; investigations on structure and function of **carotenoproteins** at the atomic level
SO Pure and Applied Chemistry (1994), 66(5), 963-72
CODEN: PACHAS; ISSN: 0033-4545
AU Jansen, F. J. H. M.; Lugtenburg, J.
AN 1995:23914 HCAPLUS
DN 122:31722

L246 ANSWER 67 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI MALATE AS ADDITIONAL SUBSTRATE FOR FATTY-ACID SYNTHESIS IN A C-4-PLANT TYPE DEVELOPED BY SALT STRESS FROM A C-3-PLANT TYPE MAIZE - A SCREENING FOR MALATE AS SUBSTRATE FOR FATTY-ACID SYNTHESIS IN CHLOROPLASTS
SO JOURNAL OF PLANT PHYSIOLOGY, (MAY 1994) Vol. 143, No. 4-5, pp. 544-549.
ISSN: 0176-1617.
AU PREISS M; KOOPMANN E; MEYER G; KOYRO H W; SCHULTZ G (Reprint)
AN 94:350525 SCISEARCH

L246 ANSWER 68 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 28
TI METABOLIC PATHWAY FOR BETA-**CAROTENE** BIOSYNTHESIS - SIMILARITIES IN THE PLANT AND ANIMAL
SO ACS SYMPOSIUM SERIES, (1994) Vol. 546, pp. 401-412.
ISSN: 0097-6156.
AU GAWIENOWSKI A M (Reprint)
AN 94:267955 SCISEARCH

L246 ANSWER 69 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 29
TI HYPER-ACCUMULATION OF ASTAXANTHIN IN A GREEN-ALGA HAEMATOCOCCUS-PLUVIALIS AT ELEVATED-TEMPERATURES
SO BIOTECHNOLOGY LETTERS, (FEB 1994) Vol. 16, No. 2, pp. 133-138.
ISSN: 0141-5492.

AU TJAHJONO A E (Reprint); HAYAMA Y; KAKIZONO T; TERADA Y; NISHIO N; NAGAI S
AN 94:192033 SCISEARCH

L246 ANSWER 70 OF 324 MEDLINE DUPLICATE 30
TI 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibition in a rat mast cell line. Impairment of tyrosine kinase-dependent signal transduction and the subsequent degranulation response.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 Jul 15) 268 (20) 15252-9.
Journal code: 2985121R. ISSN: 0021-9258.
AU Shakarjian M P; Eiseman E; Penhallow R C; Bolen J B
AN 93315510 MEDLINE

L246 ANSWER 71 OF 324 MEDLINE DUPLICATE 31
TI Family of glycosyl transferases needed for the synthesis of succinoglycan by Rhizobium meliloti.
SO JOURNAL OF BACTERIOLOGY, (1993 Nov) 175 (21) 7033-44.
Journal code: 2985120R. ISSN: 0021-9193.
AU Glucksmann M A; Reuber T L; Walker G C
AN 94042869 MEDLINE

L246 ANSWER 72 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoids** and degraded **carotenoids**. 9.
Synthesis of (S)-.alpha.-damascone
SO Tetrahedron (1993), 49(9), 1871-8
CODEN: TETRAB; ISSN: 0040-4020
AU Mori, Kenji; Amaike, Masayasu; Itou, Masamichi
AN 1993:408987 HCAPLUS
DN 119:8987

L246 ANSWER 73 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI COMPETITION OF CO2 AND **ACETATE** AS SUBSTRATES FOR FATTY-ACID SYNTHESIS IN IMMATURE CHLOROPLASTS OF BARLEY SEEDLINGS
SO JOURNAL OF PLANT PHYSIOLOGY, (NOV 1993) Vol. 142, No. 5, pp. 525-530.
ISSN: 0176-1617.
AU PREISS M (Reprint); ROSIDI B; HOPPE P; SCHULTZ G
AN 94:2910 SCISEARCH

L246 ANSWER 74 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoid production** by a green alga, Haematococcus pluvialis
SO Microbial Utilization of Renewable Resources (1993), Volume Date 1992, 8, 339-49
CODEN: MURRE6
AU Kobayashi, Makio; Kakizono, Toshihide; Nagai, Shiro
AN 1994:101500 HCAPLUS
DN 120:101500

L246 ANSWER 75 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Adhesive compsn. for fixing shoe-soles - contains polychloroprene, specified resins, silica, zinc and magnesium oxide(s), oligo-piperylene, di tert. butyl-para-cresol and organic solvent for improved strength and stability on storage.
PI SU 1754753 A1 19920815 (199331)* 4p C09J111-00
IN IRKHIN, B L; PANTUKH, B I; TUKTAROVA, L A

L246 ANSWER 76 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Reagent for treatment of water-based drilling soln. - contains calcium **acetate**, obtd. as waste from thermal wood decomposition, magnesium chloride, by-product from di methyl dioxane prodn. and water.
PI SU 1745750 A1 19920707 (199326)* 4p C09K007-02
IN ANGELOPULO, O K; AVAKOV, V E; BALABA, V I

L246 ANSWER 77 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Adhesive compsn. for adhesive tape **prodn**. - includes synthetic

isoprene rubber, glycerine ether of hydrogenated pine colophony and tetra ethoxy silane.

PI SU 1707043 A1 19920123 (199313)* 3p C09J007-02
IN ALEKSEENKO, A I; BUREEV, YU A; PARFENENKO, I D

L246 ANSWER 78 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Glycerol derivs. useful as intermediates to **isoprenoid** phospholipid(s) - obtd. e.g. from chain **isoprenoid** cpds., by reaction in presence of di isopropyl ethylamine methylene chloride with di phenyl phospho chloridate.

PI JP 04257595 A 19920911 (199243)* 7p C07C009-09
US 5221796 A 19930622 (199326) 14p C07F009-02
JP 2665630 B2 19971022 (199747) 7p C07F009-09
IN MORI, H; NISHIKAWA, N

L246 ANSWER 79 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI New long chain glycerol derivs. - useful as intermediates for biocompatible **isoprenoid** phospholipid(s).

PI JP 04257544 A 19920911 (199243)* 5p C07C069-30
US 5221796 A 19930622 (199326) 14p C07F009-02
JP 2670908 B2 19971029 (199748) 6p C07C069-30
IN MORI, H; NISHIKAWA, N

L246 ANSWER 80 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI SQUALESTATIN-1, A POTENT INHIBITOR OF SQUALENE SYNTHASE, WHICH LOWERS SERUM-CHOLESTEROL INVIVO
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (15 JUN 1992) Vol. 267, No. 17, pp. 11705-11708.
ISSN: 0021-9258.
AU BAXTER A; FITZGERALD B J; HUTSON J L; MCCARTHY A D (Reprint); MOTTERAM J M; ROSS B C; SAPRA M; SNOWDEN M A; WATSON N S; WILLIAMS R J; WRIGHT C
AN 92:371596 SCISEARCH

L246 ANSWER 81 OF 324 MEDLINE DUPLICATE 32
TI Dolichol: function, metabolism, and accumulation in human tissues.
SO BIOCHEMISTRY AND CELL BIOLOGY, (1992 Jun) 70 (6) 382-4. Ref: 28
Journal code: 8606068. ISSN: 0829-8211.
AU Carroll K K; Guthrie N; Ravi K
AN 93080867 MEDLINE

L246 ANSWER 82 OF 324 MEDLINE DUPLICATE 33
TI Fibric acid derivatives: effects on the **synthesis** of **isoprenoid** lipids in cultured human lymphocytes.
SO BIOCHIMICA ET BIOPHYSICA ACTA, (1992 Jul 29) 1127 (2) 168-73.
Journal code: 0217513. ISSN: 0006-3002.
AU Henry A; Allen C M; Stacpoole P W
AN 92353119 MEDLINE

L246 ANSWER 83 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI CHOLESTEROL-BIOSYNTHESIS AND METABOLISM
SO CARDIOVASCULAR DRUGS AND THERAPY, (APR 1992) Vol. 6, No. 2, pp. 103-110.
ISSN: 0920-3206.
AU RUSSELL D W (Reprint)
AN 92:320939 SCISEARCH

L246 ANSWER 84 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI C50 bicyclic **carotenoids**: Sarcinaxanthin **synthesis**
SO Methods in Enzymology (1992), 213(Carotenoids, Pt. A), 75-86
CODEN: MENZAU; ISSN: 0076-6879
AU Ferezou, J. P.
AN 1993:192043 HCAPLUS
DN 118:192043

L246 ANSWER 85 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

DUPLICATE 34
TI DIFLUFENICAN A **CAROTENOGENESIS** INHIBITOR ALSO REDUCES ACYL LIPID **SYNTHESIS**.
SO PESTIC BIOCHEM PHYSIOL, (1992) 43 (1), 14-21.
CODEN: PCBPBS. ISSN: 0048-3575.
AU ASHTON I P; ABULNAJA K O; PALLETT K E; COLE D J; HARWOOD J L
AN 1992:373062 BIOSIS

L246 ANSWER 86 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Compsn. for coating of multilayer paper-like material - contains film-forming polymer, achromatic pigment,dye, by-product from **isoprene** rubber **prodn**. and solvent.
PI SU 1668515 A1 19910807 (199222)* 4p D21H019-66
IN AKIM, E L; DAMASKINA, L N; RASSKAZOVA, N YA

L246 ANSWER 87 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Prepn. of cycloalkenyl alkene(s) for **carotenoid synthesis** - by dehydrating e.g. pentadienyl tri methyl cyclohexanol derivs., in presence of alkali metal bromide etc..
PI EP 454002 A 19911030 (199144)* 6p
R: AT BE CH DE FR GB IT LI NL
JP 04225952 A 19920814 (199239) 5p C07C403-12
US 5155255 A 19921013 (199244) 5p C07C403-12
EP 454002 A3 19920506 (199330) 6p
EP 454002 B1 19950628 (199530) DE 8p C07C403-12
R: AT BE CH DE DK FR GB IT LI NL
DE 59105828 G 19950803 (199536) C07C403-12
JP 2945504 B2 19990906 (199942) 6p C07C403-12
IN MAZZUCHELL, M; SOUKUP, M; SPURR, P; STIRTT, C; MAZZUCHELLI, M; STRITT, C

L246 ANSWER 88 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 35
TI A NEW PRENYLATION METHOD USING THE LITHIUM ENOLATE OF PRENAL REACTION WITH POLYUNSATURATED ALDEHYDES A SHORT ACCESS TO RETINAL.
SO TETRAHEDRON LETT, (1991) 32 (35), 4499-4500.
CODEN: TELEAY. ISSN: 0040-4039.
AU DUHAMEL L; GUILLEMONT J; POIRIER J-M
AN 1991:496993 BIOSIS

L246 ANSWER 89 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI A NEW PRENYLATION METHOD USING THE LITHIUM ENOLATE OF PRENAL - REACTION WITH POLYUNSATURATED ALDEHYDES - A SHORT ACCESS TO RETINAL
SO TETRAHEDRON LETTERS, (1991) Vol. 32, No. 35, pp. 4499-4500.
AU DUHAMEL L (Reprint); GUILLEMONT J; POIRIER J M; CHABARDES P
AN 91:490978 SCISEARCH

L246 ANSWER 90 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Stereospecific synthesis of the octaprenols WT3C4OH and WT3C3TOH
SO Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya (1991), (10), 2333-8
CODEN: IASKA6; ISSN: 0002-3353
AU Grigor'eva, N. Ya.; Pinsker, O. A.; Moiseenkov, A. M.
AN 1992:59665 HCAPLUS
DN 116:59665

L246 ANSWER 91 OF 324 MEDLINE DUPLICATE 36
TI Cell-cycle-dependent, differential prenylation of proteins.
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1991 Sep 1) 200 (2) 579-90.
Journal code: 0107600. ISSN: 0014-2956.
AU Sepp-Lorenzino L; Rao S; Coleman P S
AN 91364711 MEDLINE

L246 ANSWER 92 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI CELL-CYCLE-DEPENDENT, DIFFERENTIAL PRENYLATION OF PROTEINS
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1991) Vol. 200, No. 2, pp. 579-590.

AU SEPPLORENZINO L; RAO S; COLEMAN P S (Reprint)
AN 91:485814 SCISEARCH

L246 ANSWER 93 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 37
TI ASTAXANTHIN PRODUCTION BY A GREEN ALGA HAEMATOCOCCUS-PLUVIALIS ACCOMPANIED WITH MORPHOLOGICAL CHANGES IN **ACETATE** MEDIA.
SO J FERMENT BIOENG, (1991) 71 (5), 335-339.
CODEN: JFBIEX. ISSN: 0922-338X.
AU KOBAYASHI M; KAKIZONO T; NAGAI S
AN 1991:346391 BIOSIS

L246 ANSWER 94 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI ASTAXANTHIN PRODUCTION BY A GREEN-ALGA, HAEMATOCOCCUS-PLUVIALIS ACCOMPANIED WITH MORPHOLOGICAL-CHANGES IN **ACETATE** MEDIA
SO JOURNAL OF FERMENTATION AND BIOENGINEERING, (1991) Vol. 71, No. 5, pp. 335-339.
AU KOBAYASHI M; KAKIZONO T; NAGAI S (Reprint)
AN 91:319297 SCISEARCH

L246 ANSWER 95 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISIDUPLICATE 38
TI A GENE FROM THE PHOTOSYNTHETIC GENE-CLUSTER OF RHODOBACTER-SPHAEROIDES INDUCES TRANS-SUPPRESSION OF BACTERIOCHLOROPHYLL AND **CAROTENOID** LEVELS IN R-SPHAEROIDES AND R-CAPSULATUS
SO CURRENT MICROBIOLOGY, (1991) Vol. 23, No. 5, pp. 259-263.
AU PENFOLD R J; PEMBERTON J M (Reprint)
AN 91:602934 SCISEARCH

L246 ANSWER 96 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI EVIDENCE FOR DIRECT ABA SYNTHESIS IN DUNALIELLA VOLVOCALES.
SO CRYPTOGAM BOT, (1991) 2 (2-3), 192-200.
CODEN: CRBOEO.
AU BOPP-BUHLER M-L; WABRA P; HARTUNG W; GIMMLER H
AN 1992:101188 BIOSIS

L246 ANSWER 97 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI CHRONIC AMINOPHYLLINE ADMINISTRATION - EFFECT ON DIAPHRAGM CONTRACTILITY AND FATIGUE RESISTANCE INVITRO
SO AMERICAN REVIEW OF RESPIRATORY DISEASE, (1991) Vol. 144, No. 1, pp. 121-125.
AU KUEI J H (Reprint); SIECK G C
AN 91:406309 SCISEARCH

L246 ANSWER 98 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Prodn. of oxo-beta-ionone - by oxidn. of beta-ionone enol-**acetate** with chromium oxide soln. in sulphuric acid, in methylene chloride medium.
PI SU 1544763 A 19900223 (199102)*
IN MICROPOLSK, M A; SAMOKHVALO, G I; TUTORSKAYA, O O

L246 ANSWER 99 OF 324 MEDLINE DUPLICATE 39
TI Incorporation of squalene into rod outer segments.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1990 Aug 15) 265 (23) 13709-12.
Journal code: 2985121R. ISSN: 0021-9258.
AU Keller R K; Fliesler S J
AN 90337983 MEDLINE

L246 ANSWER 100 OF 324 MEDLINE DUPLICATE 40
TI Vitamin A metabolism in the human intestinal Caco-2 cell line.
SO BIOCHEMISTRY, (1990 Dec 18) 29 (50) 11116-23.
Journal code: 0370623. ISSN: 0006-2960.
AU Quick T C; Ong D E
AN 91105044 MEDLINE

L246 ANSWER 101 OF 324 HCAPLUS COPYRIGHT 2003 ACS

TI Polyene **synthesis**. Ready construction of retinol-**carotene** fragments, (.+-.)-6(E)-LTB3 leukotrienes, and corticrocin
SO Journal of Organic Chemistry (1990), 55(25), 6203-14
CODEN: JOCEAH; ISSN: 0022-3263
AU Wenkert, Ernest; Guo, Ming; Lavilla, Rodolfo; Porter, Barry; Ramachandran, Kishore; Sheu, Jyh Horng
AN 1991:6061 HCAPLUS
DN 114:6061

L246 ANSWER 102 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 41
TI PLASTIDIC **ISOPRENOID SYNTHESIS** DURING CHLOROPLAST DEVELOPMENT CHANGE FROM METABOLIC AUTONOMY TO A DIVISION-OF-LABOR STAGE.
SO PLANT PHYSIOL (BETHESDA), (1990) 93 (3), 1121-1127.
CODEN: PLPHAY. ISSN: 0032-0889.
AU HEINTZE A; GORLACH J; LEUSCHNER C; HOPPE P; HAGLESTEIN P; SCHULZE-SIEBERT D; SCHULTZ G
AN 1990:430889 BIOSIS

L246 ANSWER 103 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Plastidic **isoprenoid synthesis** changes from an autonomous to a division-of-labor stage during chloroplast maturation
SO Curr. Res. Photosynth., Proc. Int. Conf. Photosynth., 8th (1990), Meeting Date 1989, Volume 3, 857-60. Editor(s): Baltscheffsky, Margareta. Publisher: Kluwer, Dordrecht, Neth.
CODEN: 57BCAN
AU Heintze, Adolf; Hoppe, Petra; Hagelstein, Petra; Goerlach, Joern; Schultz, Gernot
AN 1991:446241 HCAPLUS
DN 115:46241

L246 ANSWER 104 OF 324 MEDLINE DUPLICATE 42
TI Separation of **carotenes** on cyclodextrin-bonded phases.
SO JOURNAL OF CHROMATOGRAPHY, (1990 Jan 19) 499 627-35.
Journal code: 0427043. ISSN: 0021-9673.
AU Stalcup A M; Jin H L; Armstrong D W; Mazur P; Derguini F; Nakanishi K
AN 90216947 MEDLINE

L246 ANSWER 105 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 43
TI **SYNTHESIS** OF BACTERIAL C-50 **CAROTENOID** SARCINAXANTHIN.
SO TETRAHEDRON, (1990) 46 (2), 475-486.
CODEN: TETRAB. ISSN: 0040-4020.
AU FEREZOU J P; JULIA M
AN 1990:180134 BIOSIS

L246 ANSWER 106 OF 324 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 44
TI Allylsilanes derived from .alpha.- and .beta.-ionone. Synthesis and unusual reactivity with electrophiles.
SO Tetrahedron Letters, (1989) 30/44 (6067-6070).
ISSN: 0040-4039 CODEN: TELEAY
AU Azzari E.; Faggi C.; Gelsomini N.; Taddei M.
AN 89281567 EMBASE

L246 ANSWER 107 OF 324 MEDLINE DUPLICATE 45
TI Hydroxymethylglutaryl coenzyme A reductase activity of adult Hymenolepis diminuta.
SO JOURNAL OF PARASITOLOGY, (1989 Oct) 75 (5) 653-7.
Journal code: 7803124. ISSN: 0022-3395.
AU Fioravanti C F; Kim Y; Batten C L; Weaver J R
AN 90011596 MEDLINE

L246 ANSWER 108 OF 324 MEDLINE DUPLICATE 46
TI Inhibitory effects of **carotenoids** and retinoids on the in vitro

growth of rat C-6 glioma cells.
SO PROCEEDINGS OF THE NATIONAL SCIENCE COUNCIL, REPUBLIC OF CHINA. PART B, LIFE SCIENCES, (1989 Jul) 13 (3) 176-83.
Journal code: 8502426. ISSN: 0255-6596.
AU Wang C J; Lin J K
AN 90083477 MEDLINE

L246 ANSWER 109 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Monoterpenoids transformation in Mentha leaves by means of distant hybridization
SO Proc. - Int. Congr. Essent. Oils, Fragrances Flavours, 11th (1989), Volume 3, 43-8. Editor(s): Bhattacharyya, S. C.; Sen, N.; Sethi, K. L.
Publisher: Oxford & IBH, New Delhi, India.
CODEN: 57OQAS
AU Nikolaev, A. G.; Pysova, M. T.; Lolla, L. V.
AN 1992:528309 HCAPLUS
DN 117:128309

L246 ANSWER 110 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Di hydro-cyclo-citral prodn. by acid cyclising octadienyl enol ester - useful in synthesis of perfumes, steroid(s), etc..
PI EP 255904 A 19880217 (198807)* FR 7p
JP 63044544 A 19880225 (198814)
US 4800233 A 19890124 (198906) 5p
US 4910347 A 19900320 (199017)
EP 255904 B 19910102 (199102)
DE 3766910 G 19910207 (199107)
JP 2540337 B2 19961002 (199644) 5p C07C047-32
IN SIMMONS, D P

L246 ANSWER 111 OF 324 MEDLINE DUPLICATE 47
TI **Isoprenoid synthesis** during the cell cycle. Studies of 3-hydroxy-3-methylglutaryl-coenzyme A synthase and reductase and **isoprenoid** labeling in cells synchronized by centrifugal elutriation.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1988 Jul 25) 263 (21) 10104-10.
Journal code: 2985121R. ISSN: 0021-9258.
AU Maltese W A; Sheridan K M
AN 88273097 MEDLINE

L246 ANSWER 112 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI A NUCLEAR MUTATION IN NICOTIANA-SYLVESTRIS CAUSING A THIAMIN-REVERSIBLE DEFECT IN SYNTHESIS OF CHLOROPLAST PIGMENTS.
SO PLANT PHYSIOL (BETHESDA), (1988) 88 (3), 930-935.
CODEN: PLPHAY. ISSN: 0032-0889.
AU MCHALE N A; HANSON K R; ZELITCH I
AN 1989:50772 BIOSIS

L246 ANSWER 113 OF 324 MEDLINE DUPLICATE 48
TI Prokaryotic hopanoids: the biosynthesis of the bacteriohopane skeleton. Formation of **isoprenic** units from two distinct **acetate** pools and a novel type of carbon/carbon linkage between a triterpene and D-ribose.
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1988 Aug 1) 175 (2) 405-11.
Journal code: 0107600. ISSN: 0014-2956.
AU Flesch G; Rohmer M
AN 88296507 MEDLINE

L246 ANSWER 114 OF 324 MEDLINE DUPLICATE 49
TI **Isoprenoid** biosynthesis in a marine sponge of the Amphimedon genus: incorporation studies with [1-14C] **acetate**, [4-14C] cholesterol and [2-14C] mevalonate.
SO COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY. B: COMPARATIVE BIOCHEMISTRY, (1988) 91 (2) 293-300.

Journal code: 2984730R. ISSN: 0305-0491.
AU Garson M J; Partali V; Liaaen-Jensen S; Stoilov I L
AN 89064058 MEDLINE

L246 ANSWER 115 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI End-product regulation of **carotenogenesis** in Phycomyces
SO Archives of Microbiology (1988), 150(3), 209-14
CODEN: AMICCW; ISSN: 0302-8933
AU Bejarano, Eduardo R.; Parra, Fernando; Murillo, Francisco J.; Cerda-Olmedo, Enrique
AN 1988:566998 HCAPLUS
DN 109:166998

L246 ANSWER 116 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 50
TI BETA **CAROTENE SYNTHESIS** IN ISOLATED SPINACH CHLOROPLASTS ITS TIGHT LINKAGE TO PHOTOSYNTHETIC CARBON METABOLISM.
SO PLANT PHYSIOL (BETHESDA), (1987) 84 (4), 1233-1237.
CODEN: PLPHAY. ISSN: 0032-0889.
AU SCHULZE-SIEBERT D; SCHULTZ G
AN 1987:460672 BIOSIS

L246 ANSWER 117 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 51
TI SUBSTRATE FLOW FROM PHOTOSYNTHETIC CARBON METABOLISM TO CHLOROPLAST **ISOPRENOID SYNTHESIS** IN SPINACH EVIDENCE FOR A PLASTIDIC PHOSPHOGLYCERATE MUTASE.
SO Z NATURFORSCH SECT C BIOSCI, (1987) 42 (5), 570-580.
CODEN: ZNCBDA. ISSN: 0341-0382.
AU SCHULZE-SIEBERT D; HEINTZE A; SCHULTZ G
AN 1987:299276 BIOSIS

L246 ANSWER 118 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 52
TI REGULATORY INVOLVEMENT OF PLASTIDS IN THE DEVELOPMENT OF PEROXISOMAL ENZYMES IN THE COTYLEDONS OF MUSTARD SINAPIS-ALBA L. SEEDLINGS.
SO J PLANT PHYSIOL, (1987) 126 (4-5), 421-436.
CODEN: JPPHEY.
AU BAJRACHARYA D; BERGFELD R; HATZFELD W-D; KLEIN S; SCHOPFER P
AN 1987:214249 BIOSIS

L246 ANSWER 119 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Adverse effect of .beta.-**carotene** in diet on fertility of dairy cows
SO Journal of Dairy Science (1987), 70(2), 357-66
CODEN: JDSCAE; ISSN: 0022-0302
AU Folman, Y.; Ascarelli, I.; Kraus, D.; Barash, H.
AN 1987:495736 HCAPLUS
DN 107:95736

L246 ANSWER 120 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 53
TI FULL AUTONOMY IN **ISOPRENOID SYNTHESIS** IN SPINACH CHLOROPLASTS.
SO PLANT PHYSIOL BIOCHEM (PARIS), (1987) 25 (2), 145-154.
CODEN: PPBIEX.
AU SCHULZE-SIEBERT D; SCHULTZ G
AN 1988:68961 BIOSIS

L246 ANSWER 121 OF 324 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Quantitative evaluation of .alpha.- and .beta.-adrenoceptor modulation of [3H]choline release in guinea pig superior cervical ganglia.
SO Neuroscience Letters, (1987) 73/1 (65-70).
CODEN: NELED5

AU Belluzzi O.; Travagli R.A.; Bonifazzi C.; Perri V.
AN 87039580 EMBASE

L246 ANSWER 122 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Telomerization of **isoprene** with geranyl chloride and **synthesis** of E,E-farnesyl **acetate**
SO Eesti NSV Teaduste Akadeemia Toimetised, Keemia (1986), 35(4), 269-74
CODEN: ENTKDR; ISSN: 0201-8128
AU Siirde, K.; Erm, A.; Valimae, T.; Muks, E.; Loiveke, I.; Laats, K.
AN 1988:22058 HCAPLUS
DN 108:22058

L246 ANSWER 123 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI ACID-CATALYZED CONDENSATION OF **ISOPRENE** WITH BETA ORCINALDEHYDE **SYNTHESIS** OF 2 2 DIMETHYLFORMYLCHROMANS AND SYNTHESIS OF 5 METHYLXANTHYLETIN AND SESELIN DERIVATIVES.
SO INDIAN J CHEM SECT B ORG CHEM INCL MED CHEM, (1986) 25 (1), 51-55.
CODEN: IJSBDB. ISSN: 0376-4699.
AU AHLUWALIA V K; GUPTA R
AN 1986:216991 BIOSIS

L246 ANSWER 124 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI New cyclohexenyl alkenyl carboxylic acid - mfd. by reacting retinol or retinyl **acetate** in presence of tri phenyl phosphine and aq. hydrogen halide, then reacting with glyoxylic acid.
PI JP 60231650 A 19851118 (198601)* 5p
JP 04025949 B 19920506 (199222) 5p C07C403-20

L246 ANSWER 125 OF 324 MEDLINE DUPLICATE 54
TI Suppression of murine neuroblastoma growth in vivo by mevinolin, a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.
SO JOURNAL OF CLINICAL INVESTIGATION, (1985 Nov) 76 (5) 1748-54.
Journal code: 7802877. ISSN: 0021-9738.
AU Maltese W A; Defendini R; Green R A; Sheridan K M; Donley D K
AN 86034626 MEDLINE

L246 ANSWER 126 OF 324 MEDLINE DUPLICATE 55
TI Differentiation of neuroblastoma cells induced by an inhibitor of mevalonate synthesis: relation of neurite outgrowth and acetylcholinesterase activity to changes in cell proliferation and blocked **isoprenoid synthesis**.
SO JOURNAL OF CELLULAR PHYSIOLOGY, (1985 Dec) 125 (3) 540-58.
Journal code: 0050222. ISSN: 0021-9541.
AU Maltese W A; Sheridan K M
AN 86059719 MEDLINE

L246 ANSWER 127 OF 324 MEDLINE DUPLICATE 56
TI [Inhibition of the **synthesis** of **isoprenoid** compounds by phenol precursors of the benzoquinone ring of ubiquinone]. Tormozhenie sinteza izoprenoidnykh soedinenii fenol'nymi predshestvennikami benzokhinonovogo kol'tsa ubikhinona.
SO VOPROSY MEDITSINSKOI KHIMII, (1985 Sep-Oct) 31 (5) 121-3.
Journal code: 0416601. ISSN: 0042-8809.
AU Fedurov V V
AN 86124850 MEDLINE

L246 ANSWER 128 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Electronic components encapsulated in poly arylene sulphide compsn. - contg. hydrogenated diene-mono vinyl substd. aromatic copolymer, reinforcement, filler and organosilane.
PI EP 114380 A 19840801 (198431)* EN 29p
R: AT BE CH DE FR GB IT LI LU NL SE
JP 59167040 A 19840920 (198444)
US 4514588 A 19850430 (198520)

EP 114380 B 19880203 (198805) EN
R: AT BE CH DE FR GB IT LI LU NL SE
DE 3375620 G 19880310 (198811)
JP 63025503 B 19880525 (198824)
CA 1244173 A 19881101 (198848)
IN BEEVER, W H; CHILDERS, C W; SHUE, R S

L246 ANSWER 129 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI 4-Oxo-beta ionone prodn. by oxidn. of retro ionone - with oxygen, useful as intermediate in **carotenoid synthesis**.
PI EP 101811 A 19840307 (198411)* DE 12p
R: AT BE CH DE FR GB IT LI NL
JP 59029660 A 19840216 (198413)
DK 8303217 A 19840312 (198417)
EP 101811 B 19850918 (198538) EN
R: AT BE CH DE FR GB IT LI NL
DE 3360840 G 19851024 (198544)
JP 03007665 B 19910204 (199109)
IN LOHRI, B

L246 ANSWER 130 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** and bioassay of **isoprenoid** 3-alkylthio-1,1,1-trifluoro-2-propanones: potent, selective inhibitors of juvenile hormone esterase
SO Archives of Biochemistry and Biophysics (1984), 228(2), 639-45
CODEN: ABBIA4; ISSN: 0003-9861
AU Prestwich, Glenn D.; Eng, Wai Si; Roe, R. Michael; Hammock, Bruce D.
AN 1984:81189 HCAPLUS
DN 100:81189

L246 ANSWER 131 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI CIS POLY **ISOPRENE SYNTHESIS** IN GUAYULE PLANTS PARTHENIUM-ARGENTATUM EXPOSED TO LOW NONFREEZING TEMPERATURES.
SO PLANT PHYSIOL (BETHESDA), (1984) 74 (3), 534-537.
CODEN: PLPHAY. ISSN: 0032-0889.
AU GOSS R A; BENEDICT C R; KEITHLY J H; NESSLER C L; STIPANOVIC R D
AN 1984:294272 BIOSIS

L246 ANSWER 132 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Total synthesis of 3,4,3',4'-tetradehydro-.beta.,.beta.-**carotene** -2,2'-dione
SO Acta Chemica Scandinavica, Series B: Organic Chemistry and Biochemistry (1984), B38(1), 43-7
CODEN: ACBOCV; ISSN: 0302-4369
AU Aareskjold, Kaare; Liaaen-Jensen, Synnoeve
AN 1984:472975 HCAPLUS
DN 101:72975

L246 ANSWER 133 OF 324 MEDLINE DUPLICATE 57
TI **Isoprene synthesis** in isolated embryonic Drosophila cells. I. Sterol-deficient eukaryotic cells.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1983 Jul 10) 258 (13) 8503-11.
Journal code: 2985121R. ISSN: 0021-9258.
AU Silberkang M; Havel C M; Friend D S; McCarthy B J; Watson J A
AN 83238472 MEDLINE

L246 ANSWER 134 OF 324 LIFESCI COPYRIGHT 2003 CSA DUPLICATE 58
TI Geranyl derivatives as inhibitors of the **carotenogenesis** in Synechococcus PCC 6911 (Cyanobacteria).
SO Z. NATURFORSCH., SER. C., (1983) vol. 38C, no. 5-6, pp. 387-392.
AU Juettner, F.; Bogenschuetz, O.
AN 83:34106 LIFESCI

L246 ANSWER 135 OF 324 WPIDS (C) 2003 THOMSON DERWENT

TI Prodn. of grafted copolymers as modifiers for **isoprene** rubber - by reaction of polyvinyl alcohol and epsilon-caprolactam in presence of lead **acetate**.
PI SU 969703 A 19821101 (198335)* 5p
IN KHITRIN, S V; SPASSKAYA, R I; ZILBERMAN, E N

L246 ANSWER 136 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 59
TI THE MECHANISM OF ACTION OF A CHLOROSIS INDUCING TOXIN PRODUCED BY PSEUDOMONAS-PHASEOLICOLA.
SO PLANT PHYSIOL (BETHESDA), (1982) 70 (4), 932-938.
CODEN: PLPHAY. ISSN: 0032-0889.
AU SMITH A G; RUBERY P H
AN 1983:264025 BIOSIS

L246 ANSWER 137 OF 324 MEDLINE DUPLICATE 60
TI Nutrition and carbon metabolism of Methanococcus voltae.
SO JOURNAL OF BACTERIOLOGY, (1982 Mar) 149 (3) 852-63.
Journal code: 2985120R. ISSN: 0021-9193.
AU Whitman W B; Ankwanda E; Wolfe R S
AN 82142141 MEDLINE

L246 ANSWER 138 OF 324 MEDLINE DUPLICATE 61
TI Thylakoid membrane biogenesis in Chlamydomonas reinhardtii 137+. II. Cell-cycle variations in the synthesis and assembly of pigment.
SO JOURNAL OF CELL BIOLOGY, (1982 May) 93 (2) 411-6.
Journal code: 0375356. ISSN: 0021-9525.
AU Janero D R; Barrnett R
AN 82239545 MEDLINE

L246 ANSWER 139 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Activity of several enzymes of a **carotene**- and macrotetrolide-producing actinomycete
SO Mikrobiologiya (1982), 51(2), 202-5
CODEN: MIKBA5; ISSN: 0026-3656
AU Nefelova, M. V.; Sverdlova, A. N.
AN 1982:213949 HCAPLUS
DN 96:213949

L246 ANSWER 140 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI CHARACTERISTICS OF CHLOROPHYLL FORMATION IN THE GREEN ALGA GOLENKINIA.
SO PLANT CELL PHYSIOL, (1981) 22 (6), 999-1010.
CODEN: PCPHA5. ISSN: 0032-0781.
AU ELLIS R; MOORE D; SHURE R
AN 1982:175141 BIOSIS

L246 ANSWER 141 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Stereoselective synthesis of solanesol and all-trans-decaprenol
SO Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1981), (3), 761-9
CODEN: JCPRB4; ISSN: 0300-922X
AU Sato, Kikumasa; Inoue, Seiichi; Onishi, Akira; Uchida, Nobuhiko; Minowa, Nobuto
AN 1981:569537 HCAPLUS
DN 95:169537

L246 ANSWER 142 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Studies on chloroplast autonomy in terpenoid biosynthesis
SO Berichte der Deutschen Botanischen Gesellschaft (1981), 94(1-2), 121-6
CODEN: BEDBAP; ISSN: 0365-9631
AU Grumbach, K. H.
AN 1981:600627 HCAPLUS
DN 95:200627

L246 ANSWER 143 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Adhesive for paper or polymer film **prodn**. - from butadiene -styrene and **isoprene** , rubber mixt., colophony ester, chlorinated-polyethylene and paraffin aerosil and organic solvent.
PI SU 775115 B 19801030 (198129)*
IN DUBOVITSKI, V K; LAVRINCHUK, L I; POTIEVSKAY, S A

L246 ANSWER 144 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI THE BIOCHEMISTRY OF PLANTS A COMPREHENSIVE TREATISE VOL. 4. LIPIDS STRUCTURE AND FUNCTION.
SO STUMPF, P. K. (ED.). THE BIOCHEMISTRY OF PLANTS: A COMPREHENSIVE TREATISE, VOL. 4. LIPIDS: STRUCTURE AND FUNCTION. XV+693P. ACADEMIC PRESS, INC.: NEW YORK, N.Y., USA; LONDON, ENGLAND. ILLUS. (1980) 0 (0), XV+693P.
ISBN: 0-12-675404-7.
AU STUMPF P K
AN 1981:73954 BIOSIS

L246 ANSWER 145 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 62
TI **SYNTHESIS** OF OPTICALLY ACTIVE NATURAL **CAROTENOIDS** AND STRUCTURALLY RELATED COMPOUNDS 6. **SYNTHESIS** OF PICRO CROCIN.
SO HELV CHIM ACTA, (1980) 63 (6), 1463-1466.
CODEN: HCACAV. ISSN: 0018-019X.
AU MAYER H; SANTER J-M
AN 1981:185187 BIOSIS

L246 ANSWER 146 OF 324 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI A comparison of transition metal and non-transition metal oligomerizations of **isoprene** for the **synthesis** of terpenes.
SO Annals of the New York Academy of Sciences, (1980) VOL. 333/- (286-301).
CODEN: ANYAA
AU Chalk A.J.; Magennis S.A.
AN 81067868 EMBASE

L246 ANSWER 147 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Use of the reverse osmosis method for purifying **isoprene production** wastewater
SO Khimicheskaya Promyshlennost (Moscow, Russian Federation) (1980), (2), 124-5
CODEN: KPRMAW; ISSN: 0023-110X
AU Galutkina, K. A.; Nemchenko, A. G.; Apostolova, I. V.; Karazeeva, L. N.
AN 1980:573093 HCAPLUS
DN 93:173093

L246 ANSWER 148 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI E-4-Acetoxy-2-methyl-2-butenal
SO U.S., 6 pp.
CODEN: USXXAM
IN Babler, James H.
AN 1980:93898 HCAPLUS
DN 92:93898

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4175204	A	19791120	US 1979-1075	19790108
	WO 7900485	A1	19790726	WO 1979-US28	19790116
	W: CH, DE, GB, JP, SE				
	RW: CH, DE, FR, GB				
	EP 8581	A1	19800305	EP 1979-900203	19790116
	R: CH, DE, FR, GB				

L246 ANSWER 149 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** of compounds containing the **isoprene** unit. A new stereoselective **synthesis** of all-trans vitamin A and of methyl (2E,4E)-3,7,11-trimethyldodeca-2,4-dienoate

SO Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1979), (7), 1729-33
CODEN: JCPRB4; ISSN: 0300-922X
AU Cardillo, Giuliana; Contento, Michele; Sandri, Sergio; Panunzio, Mauro
AN 1980:94599 HCAPLUS
DN 92:94599

L246 ANSWER 150 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Evidence for the existence of two .beta.-**carotene** pools and two biosynthetic .beta.-**carotene** pathways in the chloroplast
SO Zeitschrift fuer Naturforschung, C: Journal of Biosciences (1979), 34C(12), 1205-8
CODEN: ZNCBDA; ISSN: 0341-0382
AU Grumbach, K. H.
AN 1980:107386 HCAPLUS
DN 92:107386

L246 ANSWER 151 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The effect of PS II herbicides, amitrol and SAN 6706 on the activity of 3-hydroxy-3-methylglutaryl-coenzyme-A-reductase and the incorporation of [2-14C]-**acetate** and [2-3H]-mevalonate into chloroplast pigments of radish seedlings
SO Zeitschrift fuer Naturforschung, C: Journal of Biosciences (1979), 34C(11), 941-3
CODEN: ZNCBDA; ISSN: 0341-0382
AU Grumbach, K. H.; Bach, T. J.
AN 1980:19002 HCAPLUS
DN 92:19002

L246 ANSWER 152 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effect of organic substrates on chlorophyll and **carotenoid production** of Anabaena sp. under light and dark conditions
SO Journal of the Indian Botanical Society (1979), 58(4), 358-62
CODEN: JIBSAC; ISSN: 0019-4468
AU Sahu, J. K.; Adhikary, S. P.; Pattnaik, H.
AN 1981:27160 HCAPLUS
DN 94:27160

L246 ANSWER 153 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI LIPID SYNTHESIS IN IMBIBED SPORES OF THE FERN ANEMIA-PHYLLITIDIS.
SO Z PFLANZENPHYSIOL, (1979) 91 (4), 317-324.
CODEN: ZSPPAD. ISSN: 0044-328X.
AU GEMMRICH A R
AN 1979:254296 BIOSIS

L246 ANSWER 154 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The role of retinol in the initiation of sporangiophores of Phycomyces blakesleeanus
SO Planta (1979), 146(3), 257-62
CODEN: PLANAB; ISSN: 0032-0935
AU Galland, P.; Russo, V. E. A.
AN 1979:554387 HCAPLUS
DN 91:154387

L246 ANSWER 155 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of **carotene** by the yeast Sporobolomyces pararoseus T during cultivation on peat oxidate
SO Prikladnaya Biokhimiya i Mikrobiologiya (1979), 15(2), 222-6
CODEN: PBMIAK; ISSN: 0555-1099
AU Koroleva, I. F.; Zalashko, M. V.; Demina, S. G.; Kosonogova, L. V.; Evdokimova, G. A.
AN 1979:402302 HCAPLUS
DN 91:2302

L246 ANSWER 156 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 63
TI **CAROTENOID** AND STEROID **SYNTHESES** BY CARROT CELLS IN SUSPENSION CULTURE.
SO PHYSIOL PLANT, (1979) 46 (2), 127-132.
CODEN: PHPLAI. ISSN: 0031-9317.
AU SHIMIZU K; KIKUCHI T; SUGANO N; NISHI A
AN 1979:260872 BIOSIS

L246 ANSWER 157 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Selection of a nutrient medium for the production of Rhodotorula gracilis K-1 with vitamin A activity
SO Izvestiya Akademii Nauk Moldavskoi SSR, Biologicheskie i Khimicheskie Nauki (1979), (3), 56-60
CODEN: IMBKB6; ISSN: 0568-5192
AU Atamanyuk, D. I.; Borisova, T. A.; Tsygulya, T. E.; Garkavenko, A. I.
AN 1979:522112 HCAPLUS
DN 91:122112

L246 ANSWER 158 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Metal-assisted terpenoid **synthesis**. V. The catalytic trimerization of **isoprene** to trans-.beta.-farnesene and its synthetic applications for terpenoids
SO Bulletin of the Chemical Society of Japan (1978), 51(4), 1158-62
CODEN: BCSJA8; ISSN: 0009-2673
AU Akutagawa, Susumu; Taketomi, Takanao; Kumobayashi, Hidenori; Takayama, Kiyoshi; Someya, Taichi; Otsuka, Sei
AN 1978:443834 HCAPLUS
DN 89:43834

L246 ANSWER 159 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Identification of oxygen-containing organic substances from chromatographic spectra
SO Zhurnal Analiticheskoi Khimii (1978), 33(4), 775-81
CODEN: ZAKHA8; ISSN: 0044-4502
AU Vigdergauz, M. S.; Gizzatullin, R. R.; Tukmanov, R. G.; Fedin, Yu. I.; Kiyanenko, G. V.
AN 1978:484360 HCAPLUS
DN 89:84360

L246 ANSWER 160 OF 324 MEDLINE
TI [Effect of organic acids on the biosynthesis of macrotetralide antibiotics by an Actinomyces chrysomallus var. **carotenoides** strain].
Vliianie organicheskikh kislot na biosintez **makrotetralidnykh** antibiotikov shtammom Actinomyces chrysomallus var. **carotenoides**
.
SO ANTIBIOTIKI, (1978 Jul) 23 (7) 586-90.
Journal code: 0375020. ISSN: 0003-5637.
AU Nefelova M V; Sverdlova A N; Silaev A B
AN 78234086 MEDLINE

L246 ANSWER 161 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effect of organic acids on the biosynthesis of **carotenes** by Actinomyces chrysomallus strains
SO Mikrobiologiya (1978), 47(2), 208-11
CODEN: MIKBA5; ISSN: 0026-3656
AU Nefelova, M. V.; Sverdlova, A. N.; Alekseeva, L. N.
AN 1978:419961 HCAPLUS
DN 89:19961

L246 ANSWER 162 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Water soluble vinyl -**acetate** copolymer for fibres **prodn**
. - by copolymerisation with **isoprene** in presence of initiator.
PI SU 567729 A 19770831 (197824)*

IN GABRIELYAN, G A; PAKHOMOVA, A S; ROGOVIN, Z A

L246 ANSWER 163 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Symmetrical **carotenoids prodn**. - by reacting ylid cpds. with peroxy acids or their salts or esters.
PI DE 2702633 A 19770728 (197731)*
DE 2702633 C 19841025 (198444)

L246 ANSWER 164 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 64
TI ON THE INFLUENCE OF CHOLESTEROL FEEDING AND OF A LIPOGENIC DIET ON THE CHOLESTEROGENESIS IN RAT LIVER IN-VIVO.
SO HELV CHIM ACTA, (1977 (RECD 1978)) 60 (8), 2686-2694.
CODEN: HCACAV. ISSN: 0018-019X.
AU WISS O; WISS V
AN 1978:234974 BIOSIS

L246 ANSWER 165 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 65
TI ON METABOLIC DEGRADATIONS OF SQUALENE LANOSTEROL AND CHOLESTEROL IN RAT LIVER IN-VIVO EVIDENCE FOR RE CYCLING OF METABOLITES FOR THE **SYNTHESIS** OF **ISOPRENE** COMPOUNDS.
SO HELV CHIM ACTA, (1977) 60 (6), 1961-1966.
CODEN: HCACAV. ISSN: 0018-019X.
AU WISS O; WISS V
AN 1978:157927 BIOSIS

L246 ANSWER 166 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Hydroperoxide oxidation of phosphorus ylides: a new and useful route to symmetrical **carotenoids**
SO Justus Liebigs Annalen der Chemie (1977), (7), 1146-59
CODEN: JLACBF; ISSN: 0075-4617
AU Nuerrenbach, Axel; Paust, Joachim; Pommer, Horst; Schneider, Joachim; Schulz, Bernhard
AN 1978:121450 HCAPLUS
DN 88:121450

L246 ANSWER 167 OF 324 MEDLINE DUPLICATE 66
TI [Participation of **acetate** in the biosynthesis of **carotenoids** and macrotetralids by Actinomyces chrysomallus var. **carotenoides**].
Uchastie atsetata v biosinteze karotinoidov i **makrotetralidov** Actinomyces chrysomallus var. **carotenoides**.
SO MIKROBIOLOGIIA, (1977 Nov-Dec) 46 (6) 1122-3.
Journal code: 0376652. ISSN: 0026-3656.
AU Sverdlova A N; Silaev A B; Alekseeva L N; Nefelova M V
AN 78091762 MEDLINE

L246 ANSWER 168 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI PARTICIPATION OF **ACETATE** IN BIOSYNTHESIS OF **CAROTENOIDS** AND MACRO TETRALIDES BY ACTINOMYCES-CHRYSOMALLUS-VAR-**CAROTENOIDES**
.
SO MIKROBIOLOGIYA, (1977 (RECD 1978)) 44 (6), 1122-1123.
CODEN: MIKBA5. ISSN: 0026-3656.
AU SVERDLOVA A N; SILAEV A B; ALEKSEEVA L N; NEFELOVA M V
AN 1978:204223 BIOSIS

L246 ANSWER 169 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Higher **isoprenoids**. V. Partial **syntheses** from cycloartenol, cyclolaudenol. Part 1. Mangiferolic acid, ambolic acid
SO Tetrahedron (1977), 33(7), 817-19
CODEN: TETRAB; ISSN: 0040-4020
AU Singh, Chandan; Dev, Sukh
AN 1977:536027 HCAPLUS

DN 87:136027

L246 ANSWER 170 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Total **synthesis** of dl-.alpha.-tocopherol from **isoprene**
SO Eesti NSV Teaduste Akadeemia Toimetised, Keemia, Geoloogia (1977), 26(4), 271-4
CODEN: EKEGAI; ISSN: 0424-6373
AU Laats, K.; Kogerman, A.; Ammon, K.
AN 1978:136801 HCAPLUS
DN 88:136801

L246 ANSWER 171 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Optically active cyclohexane derivatives
SO Ger. Offen., 68 pp.
CODEN: GWXXBX
IN Boguth, Walter; Leuenberger, Hans G. W.; Mayer, Hans Johann; Widmer, Erich; Zell, Reinhard
AN 1976:492200 HCAPLUS
DN 85:92200

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 2537060	A1	19760304	DE 1975-2537060	19750820
	DE 2537060	B2	19790523		
	DE 2537060	C3	19800117		
	CH 605533	A	19780929	CH 1974-11434	19740821
	US 3988205	A	19761026	US 1975-601770	19750804
	JP 51082789	A2	19760720	JP 1975-99888	19750819
	JP 58007277	B4	19830209		
	FR 2303797	A1	19761008	FR 1975-25631	19750819
	FR 2303797	B1	19800725		
	BE 832565	A1	19760220	BE 1975-159309	19750820
	GB 1508195	A	19780419	GB 1975-34605	19750820
	GB 1508197	A	19780419	GB 1976-47891	19750820
	GB 1508196	A	19780419	GB 1976-47892	19750820
	AT 7506455	A	19780515	AT 1975-6455	19750820
	AT 347422	B	19781227		
	NL 7509925	A	19760224	NL 1975-9925	19750821
	NL 169195	B	19820118		
	NL 169195	C	19820616		
	JP 57011300	B4	19820303	JP 1976-452	19760101
	FR 2303786	A1	19761008	FR 1976-16821	19760603
	FR 2303786	B1	19800530		
	FR 2303798	A1	19761008	FR 1976-16822	19760603
	FR 2303798	B1	19821029		
	US 4026949	A	19770531	US 1976-707128	19760720
	US 4072715	A	19780207	US 1976-707123	19760720
	US 4095038	A	19780613	US 1976-707146	19760720
	US 4156100	A	19790522	US 1977-849138	19771107
	JP 55033463	A2	19800308	JP 1979-66908	19790531
	JP 59001692	B4	19840113		

L246 ANSWER 172 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI 4-Chloro 2-methyl crotonaldehyde **prodn**. - by chlorinating **isoprene** monoxide e.g. with tert. butyl hypochlorite, useful as vitamin A intermediate.
PI DE 2620968 A 19761118 (197648)*
US 4054608 A 19771018 (197743)
DE 2620968 B 19790607 (197924)
IT 1038011 B 19791120 (198010)

L246 ANSWER 173 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Cyclobutene derivatives as **isoprene** equivalents in terpene **synthesis**. The metathesis of 1-methylcyclobutene
SO Journal of Organic Chemistry (1976), 41(24), 3928-9

CODEN: JOCEAH; ISSN: 0022-3263
AU Wilson, Stephen R.; Schalk, David E.
AN 1976:592924 HCAPLUS
DN 85:192924

L246 ANSWER 174 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI New C5-compounds for terpene synthesis. I. Monoacetals of 2-methyl-2-butene-1,4-dial
SO Justus Liebigs Annalen der Chemie (1976), (12), 2194-205
CODEN: JLACBF; ISSN: 0075-4617
AU Paust, Joachim; Reif, Werner; Schumacher, Horst
AN 1977:121562 HCAPLUS
DN 86:121562

L246 ANSWER 175 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Bacterial **carotenoids**. LI. C50-**carotenoids**. 17. Total **synthesis** of two bacterioruberin derivatives. Absolute configuration of bacterioruberin
SO Tetrahedron Letters (1976), (12), 955-8
CODEN: TELEAY; ISSN: 0040-4039
AU Johansen, Jon E.; Liaaen-Jensen, Synnove
AN 1976:446887 HCAPLUS
DN 85:46887

L246 ANSWER 176 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The synthesis of 2,2'-dinorcarotenoids
SO Helvetica Chimica Acta (1976), 59(2), 439-52
CODEN: HCACAV; ISSN: 0018-019X
AU Kienzle, Frank; Minder, Rudolf E.
AN 1976:421660 HCAPLUS
DN 85:21660

L246 ANSWER 177 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI 2,2,6-Trimethyl-cyclohex-5-en-1,4-dione prodn - in good yields by liq phase catalytic oxidn of 3,3,5-trimethyl-cyclohex-4-en-1-one.
PI DE 2457157 A 19750612 (197525)*
NL 7415846 A 19750610 (197526)
JP 50093946 A 19750726 (197538)
FR 2253730 A 19750808 (197539)
GB 1429120 A 19760324 (197613)
US 4010205 A 19770301 (197710)
CH 585168 A 19770228 (197716)
US 4026948 A 19770531 (197723)
DE 2457157 B 19780209 (197807)
JP 53028907 B 19780817 (197837)

L246 ANSWER 178 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoid synthesis** using sulfones. **Synthesis** of apocarotenoids and a torularhodin ester
SO Helvetica Chimica Acta (1975), 58(5), 1492-7
CODEN: HCACAV; ISSN: 0018-019X
AU Fischli, Albert; Mayer, Hans
AN 1975:514676 HCAPLUS
DN 83:114676

L246 ANSWER 179 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** and reactions of **isoprenyl** terminal epoxides in the chromone and quinoline series
SO Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1975), (2), 150-4
CODEN: JCPRB4; ISSN: 0300-922X
AU Grundon, Michael F.; Okely, H. Martyn
AN 1975:170584 HCAPLUS
DN 82:170584

L246 ANSWER 180 OF 324 MEDLINE
TI Morphology and physiology of Spirochaeta aurantia strains isolated from aquatic habitats.
SO ARCHIVES OF MICROBIOLOGY, (1975 Sep 30) 105 (1) 1-12.
Journal code: 0410427. ISSN: 0302-8933.
AU Breznak J A; Canale-Parola E
AN 76060756 MEDLINE

L246 ANSWER 181 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Pivalic acid prepn from **isoprene** - by reaction with water vapour using phosphoric acid catalyst, then oxidn of pivalaldehyde.
PI JP 49024895 B 19740626 (197429)*

L246 ANSWER 182 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI **Isoprene** prepn from tert. butanol deriv - and formaldehyde using boron trifl-uoride catalyst.
PI JP 49010927 B 19740313 (197415)*

L246 ANSWER 183 OF 324 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI **SYNTHESES** OF **ISOPRENE** AND ITS INTERMEDIATES FROM 3-HYDROXY-3-METHYLBUTYL **ACETATE**
SO NIPPON KAGAKU KAISHI, (1974) Vol. 1974, No. 10, pp. 2014-2016.
AU FUKUNISH.K (Reprint); NAITO I; MASHIO F
AN 74:352428 SCISEARCH

L246 ANSWER 184 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** of **isoprene** and its intermediates from 3-hydroxy-3-methylbutyl **acetate**
SO Nippon Kagaku Kaishi (1974), (10), 2014-16
CODEN: NKAKB8; ISSN: 0369-4577
AU Fukunishi, Koushi; Naito, Ikuo; Mashio, Fujio
AN 1975:44605 HCAPLUS
DN 82:44605

L246 ANSWER 185 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** of partially hydrogenated **isoprene** dimers
SO Nippon Kagaku Kaishi (1974), (9), 1677-81
CODEN: NKAKB8; ISSN: 0369-4577
AU Imaizumi, Fumitake; Ando, Naoki; Hirayanagi, Shigetoshi; Mori, Kan
AN 1975:18258 HCAPLUS
DN 82:18258

L246 ANSWER 186 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Stereoselective coupling reactions of allylnickel complexes
SO Gazzetta Chimica Italiana (1974), 104(5-6), 557-66
CODEN: GCITA9; ISSN: 0016-5603
AU Guerrieri, Franco; Chiusoli, Gian P.; Merzoni, Sergio
AN 1974:536288 HCAPLUS
DN 81:136288

L246 ANSWER 187 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Properties of Thiocapsa roseopersicina strain BBS isolated from the estuary of the White Sea
SO Mikrobiologiya (1974), 43(2), 326-32
CODEN: MIKBA5; ISSN: 0026-3656
AU Bogorov, L. V.
AN 1974:487746 HCAPLUS
DN 81:87746

L246 ANSWER 188 OF 324 MEDLINE DUPLICATE 67
TI Nitrogen metabolism control of the **acetate**--stimulated **carotenoid synthesis** in Rhodotorula sanneii.
SO ZENTRALBLATT FUR BAKTERIOLOGIE, PARASITENKUNDE, INFEKTIONSKRANKHEITEN UND

HYGIENE. ZWEITE NATURWISSENSCHAFTLICHE ABT.: ALLGEMEINE, LANDWIRTSCHAFTLICHE UND TECHNISCHE MIKROBIOLOGIE, (1974) 129 (1) 68-71. Journal code: 0414371. ISSN: 0044-4057.
AU Vuori A T; Gyllenberg H G
AN 74304966 MEDLINE

L246 ANSWER 189 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI 3-Methylbutanediol-1,3 prodn - by catalytic oxidn. of isoamyl **acetate**, hydrogenation and saponification.
PI SU 393261 A 19731228 (197421)*

L246 ANSWER 190 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoids** and degraded **carotenoids**. II. **Synthesis** of dl-3-hydroxydihydro-.beta.-damascone and dihydro-.beta.-damascone
SO Agricultural and Biological Chemistry (1973), 37(12), 2907-11
CODEN: ABCHA6; ISSN: 0002-1369
AU Mori, Kenji; Ohki, Masahiko; Okada, Katsuhide; Takei, Yoko; Matsui, Masanao
AN 1974:83309 HCAPLUS
DN 80:83309

L246 ANSWER 191 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Synthesis of trans-4-amino-1-hydroxy-2-methyl-2-butene from **isoprene** (**synthesis** of zeatin)
SO Nippon Nogei Kagaku Kaishi (1973), 47(12), 807-11
CODEN: NNKKAA; ISSN: 0002-1407
AU Ohsugi, Motoyoshi; Takahashi, Satoru; Ichimoto, Itsuo; Ueda, Hiroo
AN 1974:403280 HCAPLUS
DN 81:3280

L246 ANSWER 192 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Use of microbial **carotene** in rations of two generations of hens in comparison with other vitamin A sources
SO Vitam. Pitan. S-kh. Zhivotn. (1973), 286-98. Editor(s): Tomme, M. F. Publisher: "Kolos", Moscow, USSR.
CODEN: 29SJA8
AU Semin, V. N.; Tkachev, I. F.; Bukhtiyarova, O. N.
AN 1975:407774 HCAPLUS
DN 83:7774

L246 ANSWER 193 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Reactions of .pi.-allylic nickel(II) bromide with organic halides. Novel synthesis of monoterpenoid compounds
SO Journal of Organic Chemistry (1972), 37(3), 462-6
CODEN: JOCEAH; ISSN: 0022-3263
AU Sato, Kikumasa; Inoue, Seichi; Ota, Satoshi; Fujita, Yoshiji
AN 1972:85936 HCAPLUS
DN 76:85936

L246 ANSWER 194 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Extension of shelf life of fresh fruits and vegetables. VIII. Effect of packaging in polyethylene bags on incorporation of 2-14C-mevalonic acid and 2-14C-**acetate** into tomato **carotenoids**
SO Journal of the Japanese Society for Horticultural Science (1972), 41(1), 92-7
CODEN: EGKZA9; ISSN: 0013-7626
AU Okubo, Masutaro; Umeda, Keiji
AN 1972:486729 HCAPLUS
DN 77:86729

L246 ANSWER 195 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effect of potassium and sodium acetates on pigment production in Staphylococcus aureus 209-P

SO Mikrobiologiya (1971), 40(6), 1112-13
CODEN: MIKBA5; ISSN: 0026-3656
AU Ignatov, V. V.; Stupnikova, S. K.; Volkova, V. V.
AN 1972:122238 HCAPLUS
DN 76:122238

L246 ANSWER 196 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effects of beta-**carotene**, vitamin A, and glucocorticoids on collagen synthesis in wounds
SO Proceedings of the Society for Experimental Biology and Medicine (1971), 137(3), 936-8
CODEN: PSEBAA; ISSN: 0037-9727
AU Ehrlich, H. Paul; Tarver, H.
AN 1971:461125 HCAPLUS
DN 75:61125

L246 ANSWER 197 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI **CAROTENOID SYNTHESIS** IN A SUSPENSION CULTURE OF CARROT-D CELLS.
SO PLANT CELL PHYSIOL, (1971) 12 (4), 525-531.
CODEN: PCPHA5. ISSN: 0032-0781.
AU SUGANO N; MIYA S; NISHI A
AN 1972:139862 BIOSIS

L246 ANSWER 198 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Regulation of the synthesis of metabolites synthesized via acetyl-coenzyme A in a culture of Streptomyces erythraeus
SO Mikrobiologiya (1971), 40(2), 246-51
CODEN: MIKBA5; ISSN: 0026-3656
AU Bezborodov, A. M.; Galynkin, V. A.
AN 1971:431601 HCAPLUS
DN 75:31601

L246 ANSWER 199 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Research, conducted at the All-Union Scientific-Research Institute of Synthetic Rubber, on the preparation of basic monomers for the synthesis of rubbers
SO Kauchuk i Rezina (1971), 30(2), 15-17
CODEN: KCRZAE; ISSN: 0022-9466
AU Gorin, Yu. A.
AN 1971:143011 HCAPLUS
DN 74:143011

L246 ANSWER 200 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Nonconjugated dienes
SO Jpn. Tokkyo Koho, 2 pp.
CODEN: JAXXAD
IN Hata, Go; Aoki, Kazumi
AN 1972:15566 HCAPLUS
DN 76:15566

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 45007526	B4	19700316	JP	19650809

L246 ANSWER 201 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Utilization of malonyl-CoA for the biosynthesis of .beta.-**carotene** and ergosterol in cell-free preparations from Blakeslea trispora
SO Acta Chemica Scandinavica (1947-1973) (1970), 24(7), 2361-5
CODEN: ACSAA4; ISSN: 0001-5393
AU Neujahr, Halina Y.; Bjork, Lars
AN 1971:60949 HCAPLUS
DN 74:60949

L246 ANSWER 202 OF 324 HCAPLUS COPYRIGHT 2003 ACS

TI Structure and **synthesis** of new phenolic **carotenoids** from Streptomyces mediolani
SO Gazzetta Chimica Italiana (1970), 100(6), 581-90
CODEN: GCITA9; ISSN: 0016-5603
AU Arcamone, Federico; Camerion, Bruno; Franceschi, Giovanni; Penco, Sergio
AN 1971:23040 HCAPLUS
DN 74:23040

L246 ANSWER 203 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Anaerobic growth of purple nonsulfur bacteria under dark conditions
SO Journal of Bacteriology (1970), 104(1), 462-72
CODEN: JOBAAY; ISSN: 0021-9193
AU Uffen, Robert L.; Wolfe, Ralph S.
AN 1970:517618 HCAPLUS
DN 73:117618

L246 ANSWER 204 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI BIOCHEMICAL ASPECTS OF FUNGAL DIFFERENTIATION NEUROSPORA MODEL.
SO PHYSIOL VEG, (1970) 8 (3), 375-386.
CODEN: PHYVAP. ISSN: 0031-9368.
AU TURIAN G
AN 1971:147220 BIOSIS

L246 ANSWER 205 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Reagent for the detection of acetylene derivatives on thin-layer plates
SO Journal of Chromatography (1970), 49(2), 317-22
CODEN: JOCRAM; ISSN: 0021-9673
AU Schulte, Karl E.; Ruecker, G.
AN 1970:484464 HCAPLUS
DN 73:84464

L246 ANSWER 206 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Use of a polarographic method in controlling vitamin production
SO Problemy Analiticheskoi Khimii (1970), 1, 177-84
CODEN: PYAKAP; ISSN: 0370-2677
AU Devyatnin, V. A.; Solunina, I. A.
AN 1971:146292 HCAPLUS
DN 74:146292

L246 ANSWER 207 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Catalytic ene **synthesis** with carbonyl compounds. Addition of **isoprene** to formaldehyde
SO Doklady Akademii Nauk SSSR (1970), 190(1), 102-3 [Chem]
CODEN: DANKAS; ISSN: 0002-3264
AU Klimova, E. I.; Arbuzov, Yu. A.
AN 1970:111143 HCAPLUS
DN 72:111143

L246 ANSWER 208 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effectiveness of various sources of vitamin A in poultry rations
SO Vestnik Sel'skokhozyaistvennoi Nauki (Moscow) (1970), 15(9), 73-82
CODEN: VSNLAF; ISSN: 0206-6335
AU Tkachev, I. F.; Semin, V. N.; Bukhtiyarova, O. N.
AN 1971:10902 HCAPLUS
DN 74:10902

L246 ANSWER 209 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Catalytic oxidative dehydrogenation reaction of hydrocarbons. III. **Production** of **isoprene** by oxidative dehydrogenation
SO Kogyo Kagaku Zasshi (1969), 72(12), 2571-7
CODEN: KGKZA7; ISSN: 0368-5462
AU Nishikawa, Eiichiro; Ueki, Toru; Mori, Goichi; Morita, Yoshiro
AN 1970:99910 HCAPLUS
DN 72:99910

L246 ANSWER 210 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of .beta.-**carotene** by cell-free extracts of Phycomyces blakesleeanus
SO Journal of Biological Chemistry (1969), 237, 681-6
CODEN: JBCHA3; ISSN: 0021-9258
AU Yokoyama, H.; Nakayama, T. O. M.; Chichester, C. O.
AN 1962:405959 HCAPLUS
DN 57:5959
OREF 57:1273b-e

L246 ANSWER 211 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Natural [poly(**isoprenyl**)]phenols. **Synthesis** of grifolin and ostruthin
SO Gazzetta Chimica Italiana (1969), 99(3), 308-15
CODEN: GCITA9; ISSN: 0016-5603
AU Cardillo, Giuliana; Cricchio, Renato; Merlini, Lucio; Nasini, Gianluca
AN 1969:422201 HCAPLUS
DN 71:22201

L246 ANSWER 212 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Function of sterols in Mycoplasma
SO Abhandlungen der Deutschen Akademie der Wissenschaften zu Berlin, Klasse fuer Medizin (1969), Volume Date 1968, No. 2, 37-45
CODEN: ADWMAX; ISSN: 0568-4250
AU Smith, Paul Francis
AN 1969:457813 HCAPLUS
DN 71:57813

L246 ANSWER 213 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Radioisotopic studies on the biosynthesis of the glyceryl diether lipids of Halobacterium cutirubrum
SO Canadian Journal of Biochemistry (1968), 46(8), 971-7
CODEN: CJBIAE; ISSN: 0008-4018
AU Kates, M.; Wassef, M. K.; Kushner, D. J.
AN 1968:457576 HCAPLUS
DN 69:57576

L246 ANSWER 214 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of N6-(.DELTA.2-isopentenyl)adenosine. Precursor relation of **acetate** and mevalonate to the .DELTA.2-isopentenyl group of the transfer ribonucleic acid of microorganisms
SO Biochemistry (1968), 7(3), 940-4
CODEN: BICHAW; ISSN: 0006-2960
AU Fittler, Fritz; Kline, Larry K.; Hall, Ross Hume
AN 1968:84264 HCAPLUS
DN 68:84264

L246 ANSWER 215 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effect of previous illumination time of etiolated leaves of Spirodela polyrrhiza on the radioactivity in **carotenoids**, due to sodium **acetate**-2-14C, incorporation in the dark
SO Comptes Rendus des Seances de l'Academie des Sciences, Serie D: Sciences Naturelles (1968), 267(7), 733-6
CODEN: CHDDAT; ISSN: 0567-655X
AU Moneger, Rene
AN 1969:896 HCAPLUS
DN 70:896

L246 ANSWER 216 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of .beta.-**carotene** from one-carbon units
SO Pharmazie (1968), 23(10), 594
CODEN: PHARAT; ISSN: 0031-7144
AU Reichel, Ludwig; Schreiber, Gerhard

AN 1969:17697 HCAPLUS
DN 70:17697

L246 ANSWER 217 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effect of light on **carotenoid** biosynthesis in Spirodela polyrrhiza
SO Physiologie Vegetale (1968), 6(2), 165-202
CODEN: PHYVAP; ISSN: 0031-9368
AU Moneger, Rene
AN 1968:457482 HCAPLUS
DN 69:57482

L246 ANSWER 218 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Secondary **carotenoids** in green algae. I. Chemistry, occurrence, and factors controlling the biogenesis of these polyenes
SO (1968), 61(1), 81-102
AU Czygan, Franz C.
AN 1968:93812 HCAPLUS
DN 68:93812

L246 ANSWER 219 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Thermal decomposition of trimethylethylene glycol acetates
SO Azerbaidzhanskii Khimicheskii Zhurnal (1968), (1), 61-3
CODEN: AZKZAU; ISSN: 0005-2531
AU Movsumzade, M. M.; Ismailova, F. E.
AN 1968:486231 HCAPLUS
DN 69:86231

L246 ANSWER 220 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Purification of waste water in the first step of **isoprene synthesis** from isobutylene and formaldehyde
SO U.S.S.R.
From: Izobret., Prom. Obraztsy, Tovarnye Znaki 1967, 44(6), 188.
CODEN: URXXAF
IN Zheleznyak, A. S.; Nemtsov, M. S.; Ogorodnikov, S. K.; Lesteva, T. M.; Pokorskii, V. N.; Trenke, K. M.; Shapiro, L. P.; Yablochkina, M. N.
AN 1968:81248 HCAPLUS
DN 68:81248

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	SU 193367		19670302	SU	19640603

L246 ANSWER 221 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI 4-Hydroxyretinal
SO Fr., 3 pp.
CODEN: FRXXAK
IN Reedy, Albert J.
AN 1968:29903 HCAPLUS
DN 68:29903

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 1484573		19670609		

L246 ANSWER 222 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Cyclization of dehydronerolidol **acetate** as a route to the **synthesis** of cyclic **isoprenoids**
SO Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya (1967), (5), 1144-6
CODEN: IASKA6; ISSN: 0002-3353
AU Semenovskii, A. V.; Smit, V. A.; Chernova, T. N.; Kucherov, V. F.
AN 1968:2997 HCAPLUS
DN 68:2997

L246 ANSWER 223 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Bacterial **carotenoids**. XXIII. **Carotenoids** of

Thiorhodaceae. 6. Total **synthesis** of okenone and related compounds
SO Acta Chemica Scandinavica (1947-1973) (1967), 21(4), 970-82
CODEN: ACSAA4; ISSN: 0001-5393
AU Aasen, Arne J.; Liaaen Jensen, Synnoeve
AN 1967:473716 HCAPLUS
DN 67:73716

L246 ANSWER 224 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effect of dietary cholesterol and ubiquinone on **isoprene synthesis** in rativer
SO Archives of Biochemistry and Biophysics (1967), 121(1), 147-53
CODEN: ABBIA4; ISSN: 0003-9861
AU Krishnaiah, K. V.; Joshi, V. C.; Ramasarma, T.
AN 1967:451879 HCAPLUS
DN 67:51879

L246 ANSWER 225 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biological activity of **carotenoids** in the bird
SO Zentralblatt fuer Veterinaermedizin, Reihe A (1967), 14(2), 119-28
CODEN: ZVRAAX; ISSN: 0300-8711
AU Prohaszka, Laszlo; Toth, Marton
AN 1967:419023 HCAPLUS
DN 67:19023

L246 ANSWER 226 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Telomerization reaction of **isoprene** with acetic acid
SO Eesti NSV Teaduste Akadeemia Toimetised, Keemia, Geoloogia (1967), 16(1), 37-47
CODEN: EKEGAI; ISSN: 0424-6373
AU Erm, A.; Laats, K.
AN 1967:490950 HCAPLUS
DN 67:90950

L246 ANSWER 227 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Mechanism of diene C5H8 (**isoprene**) **production** in illuminated leaves
SO Fiziologiya Rastenii (Moscow) (1966), 13(5), 753-61
CODEN: FZRSAV; ISSN: 0015-3303
AU Sanadze, G. A.
AN 1967:8846 HCAPLUS
DN 66:8846

L246 ANSWER 228 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Influence of lipid components of Mycoplasma laidlawii membranes on osmotic fragility of cells
SO Journal of Bacteriology (1966), 91(2), 609-16
CODEN: JOBAAY; ISSN: 0021-9193
AU Razin, S.; Tourtellotte, M. E.; McElhaney, R. N.; Pollack, J. D.
AN 1966:53896 HCAPLUS
DN 64:53896
OREF 64:10115b-d

L246 ANSWER 229 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Role of **carotenoids** in egg **production** and in the liveability of baby chicks
SO Magyar Allatorvosok Lapja (1966), 21(12), 552-5
CODEN: MGALA5; ISSN: 0025-004X
AU Prohaszka, Laszlo; Toth, Marton
AN 1967:83546 HCAPLUS
DN 66:83546

L246 ANSWER 230 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** in the **carotenoids** series. XX. Novel

syntheses of apocarotenoids
SO Helvetica Chimica Acta (1966), 49(1), 369-90
CODEN: HCACAV; ISSN: 0018-019X
AU Schwieter, U.; Gutmann, H.; Lindlar, H.; Marret, R.; Rigassi, N.; Ruegg, R.; Schaeren, S. F.; Isler, O.
AN 1966:68009 HCAPLUS
DN 64:68009
OREF 64:12734b-h,12735a-d

L246 ANSWER 231 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** of **carotenoidal** compounds. II. Preparation of polyene(benzo)fulvenes
SO Recueil des Travaux Chimiques des Pays-Bas (1966), 85(3), 339-42
CODEN: RTCPA3; ISSN: 0165-0513
AU Haeck, H. H.; Kralt, T.
AN 1966:420974 HCAPLUS
DN 65:20974
OREF 65:3915g-h,3916a-c

L246 ANSWER 232 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biogenesis of **carotenoids** in Trentepohlia aurea
SO Zeitschrift fuer Pflanzenphysiologie (1966), 55(1), 59-64
CODEN: ZSPPAD; ISSN: 0044-328X
AU Czygan, Franz Christian; Kalb, Klaus
AN 1966:475605 HCAPLUS
DN 65:75605
OREF 65:14151e-f

L246 ANSWER 233 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Comtemporary notions on the biosynthesis of **carotenoids**
SO Ukrains'kii Botanichnii Zhurnal (1966), 23(2), 3-11
From: Ref. Zh., Biol. Khim. 1967, Abstr. No. 2F803
CODEN: UKBZAW; ISSN: 0372-4123
AU Drokova, G.
AN 1967:112109 HCAPLUS
DN 66:112109

L246 ANSWER 234 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Quaternary ionylidenethylphosphonium salts
SO 11 pp.
IN Nuerrenbach, Axel; Sarnecki, Wilhelm; Reif, Werner
AN 1965:498600 HCAPLUS
DN 63:98600
OREF 63:18156c-f

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 1395458		19650409	FR	

L246 ANSWER 235 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Xanthones. VI. Claisen rearrangements, selective demethylations, and synthesis of dihydroisojacareubin and alvaxanthone trimethyl ether
SO Tetrahedron (1965), 21(9), 2653-69
CODEN: TETRAB; ISSN: 0040-4020
AU Burling, E. D.; Jefferson, A.; Scheinmann, F.
AN 1965:498140 HCAPLUS
DN 63:98140
OREF 63:18011a-h,18012a-e

L246 ANSWER 236 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoids** and related compounds. XI. **Syntheses** of .delta.-**carotene** and .epsilon.-**carotene**
SO Journal of the Chemical Society, Abstracts (1965), (March), 2019-26
CODEN: JCSAAZ; ISSN: 0590-9791
AU Manchand, P. S.; Ruegg, R.; Schwieter, U.; Siddons, P. T.; Weedon, B. C.

L.
AN 1965:74391 HCAPLUS
DN 62:74391
OREF 62:13187b-d

L246 ANSWER 237 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Comparative biosynthesis of mevalonic acid by Mycoplasma
SO Journal of Bacteriology (1965), 89(1), 146-53
CODEN: JOBAAY; ISSN: 0021-9193
AU Smith, Paul F.; Henrikson, C. V.
AN 1965:24065 HCAPLUS
DN 62:24065
OREF 62:4353e-g

L246 ANSWER 238 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Vitamin A and **isoprenoid synthesis** in the rat
SO Biochemical Journal (1965), 95(1), 138-43
CODEN: BIJOAK; ISSN: 0264-6021
AU Diplock, A. T.; Green, J.; Bunyan, J.
AN 1965:61219 HCAPLUS
DN 62:61219
OREF 62:10899c-d

L246 ANSWER 239 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The lipase and pigments of staphylococci
SO Annals of the New York Academy of Sciences (1965), 128(1), 132-51
CODEN: ANYAA9; ISSN: 0077-8923
AU Stewart, Gordon T.
AN 1965:501202 HCAPLUS
DN 63:101202
OREF 63:18681b-d

L246 ANSWER 240 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of ubiquinone (coenzyme Q) in microorganisms
SO Bulletin of the National Institute of Sciences of India (1965), No. 28, 25-31
CODEN: BNSIAE; ISSN: 0027-9528
AU Jayaraman, J.; Raman, Tarakad S.
AN 1967:26725 HCAPLUS
DN 66:26725

L246 ANSWER 241 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** of .beta.-**carotene** and **lycopene** from 4-octene-2,7-dione
SO Justus Liebigs Annalen der Chemie (1965), 684, 14-24
CODEN: JLACBF; ISSN: 0075-4617
AU Kabbe, Hans Joachim; Truscheit, Ernst; Eiter, Karl
AN 1965:431860 HCAPLUS
DN 63:31860
OREF 63:5688e-h,5689a-c

L246 ANSWER 242 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoids** and related compounds. XII. **Synthesis** of chlorobactene, "HO-chlorobactene" and rhodopin
SO Acta Chemica Scandinavica (1964), 18(7), 1739-44
CODEN: ACHSE7; ISSN: 0904-213X
AU Bonnett, R.; Spark, A. A.; Weedon, B. C. L.
AN 1965:439278 HCAPLUS
DN 63:39278
OREF 63:7052f-h,7053a-e

L246 ANSWER 243 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI 3-Methyl-3-buten-1-ol **acetate** and **isoprene** glycol diacetate

SO 3 pp.
AN 1963:415164 HCAPLUS
DN 59:15164
OREF 59:2653h,2654a

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 918962		19630220	GB	

L246 ANSWER 244 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Vitamin A intermediates
SO 6 pp.
IN Truscheit, Ernst; Eiter, Karl; Oediger, Hermann; Stein, Eberhard; Kabbe, Hans J.; Lorenz, Rudolf
AN 1963:468787 HCAPLUS
DN 59:68787
OREF 59:12661f-h,12662a

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 1149353		19630530	DE	19600803
	GB 952498			GB	
	US 3247239		1966	US	

L246 ANSWER 245 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Asymmetrical incorporation of **acetate**-14C into .beta.-**carotene** bio-**synthesized** by Phycomyces blakesleeanus
SO Proceedings of the Society for Experimental Biology and Medicine (1963), 114, 444-7
CODEN: PSEBAA; ISSN: 0037-9727
AU Lotspeich, F. J.; Krause, R. F.; Lilly, V. G.; Barnett, H. L.
AN 1964:32973 HCAPLUS
DN 60:32973
OREF 60:5916g-h

L246 ANSWER 246 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The incorporation of C14O2 **acetate**-2-C14, and mevalonate-2-C14 into the **carotenoids** of mature tomato leaves
SO Ann. Physiol. Vegetale (1963), 5(2), 115-40
AU Costes, C.
AN 1963:464175 HCAPLUS
DN 59:64175
OREF 59:11895g-h,11896a

L246 ANSWER 247 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Action of diterpene alcohols on the biosynthesis of **carotenoids** and phytol, using **acetate**-2-C14 in maize plantules
SO Compt. Rend. (1962) 355-7
AU Costes, Claude
AN 1962:485298 HCAPLUS
DN 57:85298
OREF 57:17082h-i

L246 ANSWER 248 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The effect of diphenylamine on **carotenoid**, sterol, and fatty acid **synthesis** in Phycomyces blakesleeanus
SO Archives of Biochemistry and Biophysics (1962), 97, 138-45
CODEN: ABBIA4; ISSN: 0003-9861
AU Olson, James Allen; Knizley, Homer, Jr.
AN 1962:412893 HCAPLUS
DN 57:12893
OREF 57:2657c-e

L246 ANSWER 249 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Partial **syntheses** of **carotenes** by means of lead tetraacetate

SO Rev. Chim., Acad. Rep. Populaire Roumaine (1962), 7(1), 79-84
AU Bodea, C.; Nicoara, E.
AN 1963:435760 HCAPLUS
DN 59:35760
OREF 59:6450f-h

L246 ANSWER 250 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Improvement in synthesis of vitamin A acid and related compounds
IN Pommer, Horst; Sarnecki, Wilhelm
AN 1962:67055 HCAPLUS
DN 56:67055
OREF 56:12960g-i,12961a-i,12962a-i,12963a,12964a

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 3006939		19611031	US	

L246 ANSWER 251 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Influence of insect lures on hyphal growth and sporulation of Choanephora trispora
SO Canadian Journal of Microbiology (1961), 7, 807-13
CODEN: CJMIAZ; ISSN: 0008-4166
AU Zajic, James E.; Kuehn, H. H.
AN 1962:33992 HCAPLUS
DN 56:33992
OREF 56:6468c-f

L246 ANSWER 252 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Mevalonic acid and **carotenogenes** in carrot extracts
SO Naturwissenschaften (1961), 48, 738-9
CODEN: NATWAY; ISSN: 0028-1042
AU Modi, V. V.; Patwa, D. K.
AN 1962:80803 HCAPLUS
DN 56:80803
OREF 56:15806f-g

L246 ANSWER 253 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Acetate** incorporation into the **carotenoids** of Chromatium
SO Biochimica et Biophysica Acta (1961), 54, 525-32
CODEN: BBACAQ; ISSN: 0006-3002
AU Benedict, C. R.; Fuller, R. C.; Bergeron, J. A.
AN 1962:55919 HCAPLUS
DN 56:55919
OREF 56:10683h-i

L246 ANSWER 254 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Glucose as a carbon source for **carotene synthesis** in tomatoes
SO Archives of Biochemistry and Biophysics (1961), 93, 231-7
CODEN: ABBIA4; ISSN: 0003-9861
AU Purcell, Albert E.; Thompson, Guy A., Jr.
AN 1961:112745 HCAPLUS
DN 55:112745
OREF 55:21255c-e

L246 ANSWER 255 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Factors affecting the **production** of **carotene** by Choanephora cucurbitarum
SO Mycologia (1961), Volume Date 1960, 52, 80-96
CODEN: MYCOAE; ISSN: 0027-5514
AU Chu, F. S.; Lilly, Virgil Greene
AN 1962:55975 HCAPLUS
DN 56:55975
OREF 56:10696b-f

L246 ANSWER 256 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Enzymic **synthesis** of **carotenoids** in cell-free extracts of carrot
SO Enzymologia (1961), 23, 27-34
CODEN: ENZYAS; ISSN: 0013-9424
AU Modi, V. V.; Patwa, D. K.
AN 1961:100109 HCAPLUS
DN 55:100109
OREF 55:18888e

L246 ANSWER 257 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI .gamma.,.gamma.-Dimethylallyl **acetate**
IN Samokhvalov, G. I.; Miropol'skaya, M. A.; Fedotova, N. I.; Anosov, V. I.; Nashatyrev, A. N.; Savostin, A. P.
AN 1960:80369 HCAPLUS
DN 54:80369
OREF 54:15248g-i

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	SU 125800		19600201	SU	

L246 ANSWER 258 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Enzymic **synthesis** and destruction of **carotenoids** in mango extracts
SO Experientia (1960), 16, 352
CODEN: EXPEAM; ISSN: 0014-4754
AU Modi, V. V.; Patwa, D. K.
AN 1961:23351 HCAPLUS
DN 55:23351
OREF 55:4663a-b

L246 ANSWER 259 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoid syntheses**. XXVIII. **Syntheses** of 4-hydroxy derivatives of .beta.-apocarotenals and .beta.-apocarotenic acids as well as the preparation of 3,4-dehydro-.beta.-apocarotenals and 3,4-dehydro-.beta.-apocarotenic acids
SO Helvetica Chimica Acta (1960), 43, 94-101
CODEN: HCACAV; ISSN: 0018-019X
AU Entschel, R.; Karrer, P.
AN 1961:131429 HCAPLUS
DN 55:131429
OREF 55:24822b-f

L246 ANSWER 260 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The **production** of **carotene** by Phycomyces blakesleeanus. II. The **production** of radioactive .beta.-**carotene** by using Phycomyces blakesleeanus
SO West Va., Univ. Agr. Expt. Sta., Bull. (1960), No. 441T, 61-76
From: Biol. Abstr. 35, Abstr. No. 64209(1960).
AU Lilly, Virgil Greene; Barnett, H. L.; Krause, R. F.
AN 1961:138181 HCAPLUS
DN 55:138181
OREF 55:26134i,26135a-b

L246 ANSWER 261 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** of oxygenated **carotenoids**
SO Voprosy Khim. Terpenov i Terpenoidov, Akad. Nauk Litovsk. S.S.R., Trudy Vsesoyuz. Soveshchaniya, Vil'nyus (1960), Volume Date 1959 43-9
AU Samokhvalov, G. I.; Vakulova, L. A.
AN 1961:93066 HCAPLUS
DN 55:93066
OREF 55:17490g-i

L246 ANSWER 262 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenogenesis**. XXVI. The incorporation of **acetate** -C14, mevalonate-C14 and C14O2 into .beta.-**carotene** by the fungus Phycomyces blakesleeanus
SO Biochemical Journal (1960), 76, 5-10
CODEN: BIJOAK; ISSN: 0264-6021
AU Braithwaite, G. D.; Goodwin, T. W.
AN 1960:130324 HCAPLUS
DN 54:130324
OREF 54:25062f-h

L246 ANSWER 263 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenogenesis**. XXV. The incorporation of **acetate** -1-C14, **acetate**-2-C14 and C14O2 into **lycopene** by tomato slices
SO Biochemical Journal (1960), 76, 1-5
CODEN: BIJOAK; ISSN: 0264-6021
AU Braithwaite, G. D.; Goodwin, T. W.
AN 1960:130323 HCAPLUS
DN 54:130323
OREF 54:25062d-f

L246 ANSWER 264 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of **carotenes** in carrot extracts
SO Nature (London, United Kingdom) (1959), 184(Suppl. No.13), 983-4
CODEN: NATUAS; ISSN: 0028-0836
AU Modi, V. V.; Patwa, D. K.
AN 1960:63306 HCAPLUS
DN 54:63306
OREF 54:12276c-d

L246 ANSWER 265 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** in the **carotenoid** series. XV. **Syntheses** in the .beta., **carotenal** and .beta.-**carotenol** series
SO Helvetica Chimica Acta (1959), 42, 854-64
CODEN: HCACAV; ISSN: 0018-019X
AU Ruegg, R.; Montavon, M.; Ryser, G.; Saucy, G.; Schwieter, U.; Isler, O.
AN 1960:2428 HCAPLUS
DN 54:2428
OREF 54:625b-i

L246 ANSWER 266 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Comparison of the incorporation of labeled CO2, **acetate** and mevalonate into **carotenoids** in a number of **carotenogenic** systems
SO C I B A Foundation Symposium Biosynthesis of Terpenes and Sterols (1959), Volume Date 1958 279-91, discussion 291-4
AU Goodwin, T. W.
AN 1960:17695 HCAPLUS
DN 54:17695
OREF 54:3602d-i,3603a

L246 ANSWER 267 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of **carotenoids** by microorganisms
SO Ciba Foundation Symposium Biosynthesis of Terpenes and Sterols (1959), Volume Date 1958 267-76, discussion 277-8
AU Grob, E. C.
AN 1960:29345 HCAPLUS
DN 54:29345
OREF 54:5810a-d

L246 ANSWER 268 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI .beta.-**Carotene** fermentation

SO Rept. Taiwan Sugar Expt. Sta. (Taiwan) (1959), 20, 91-100
From: Biol. Abstr. 36, Abstr. No. 18343(1961).
AU Su, K. C.
AN 1962:471698 HCAPLUS
DN 57:71698
OREF 57:14290a-c

L246 ANSWER 269 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Thermal rearrangement of ergosterol peroxide
SO Ann. (1959), 620, 46-62
AU Bergmann, Werner; Meyers, Martin B.
AN 1959:112015 HCAPLUS
DN 53:112015
OREF 53:20132i,20133a-i,20134a

L246 ANSWER 270 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoid syntheses**. XXIV. Further reactions of .beta.- and .alpha.-**carotene** with bromosuccinimide
SO Helvetica Chimica Acta (1958), 41, 983-7
CODEN: HCACAV; ISSN: 0018-019X
AU Entschel, R.; Karrer, P.
AN 1958:113912 HCAPLUS
DN 52:113912
OREF 52:20234h-i,20235a-b

L246 ANSWER 271 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenogenesis**. XXV. The incorporation of C14-carbon dioxide, **acetate**-C14, and mevalonate-C14 into .beta.-**carotene** by illuminated etiolated maize seedlings
SO Biochemical Journal (1958), 70, 612-17
CODEN: BIJOAK; ISSN: 0264-6021
AU Goodwin, T. W.
AN 1959:12402 HCAPLUS
DN 53:12402
OREF 53:2367c-f

L246 ANSWER 272 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenoid** biosynthesis in tomatoes
SO Proceedings of the American Society for Horticultural Science (1958), 71, 349-55
CODEN: PASHA6; ISSN: 0099-4065
AU Francis, F. J.
AN 1958:105417 HCAPLUS
DN 52:105417
OREF 52:18692i,18693a-b

L246 ANSWER 273 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The chemical mechanism of acetoacetic acid synthesis in the liver
SO Biochemische Zeitschrift (1958), 330, 269-95
CODEN: BIZEA2; ISSN: 0366-0753
AU Lynen, Feodor; Henning, Ulf; Bublitz, Clark; Sorbo, Bo; Kroplin-Rueff, Luistraud
AN 1961:60388 HCAPLUS
DN 55:60388
OREF 55:11586a-e

L246 ANSWER 274 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effect of light and temperature on the **production** of **carotenoid** pigments by + and - sexes of Phycomyces blakes-leeanus
SO Proc. West Va. Acad. Sci. (1958), Volume Date 1957-1958, 29/30, 25-31
AU Lilly, V. G.; Barnett, H. L.; Krause, R. F.
AN 1960:23855 HCAPLUS
DN 54:23855
OREF 54:4771g-i,4772a

L246 ANSWER 275 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Unsaturated compounds
AN 1958:6619 HCAPLUS
DN 52:6619
OREF 52:1223i,1224a-c

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 775060		19570515	GB	
	US 2917539		1959	US	

L246 ANSWER 276 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Total **synthesis** of **isoprenoid** alcohols
SO Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya (1957) 1267-70
CODEN: IASKA6; ISSN: 0002-3353
AU Nazarov, I. N.; Gusev, B. P.; Gunar, V. I.
AN 1958:34658 HCAPLUS
DN 52:34658
OREF 52:6150h-i,6151a-g

L246 ANSWER 277 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** in the **carotenoid** series. VIII. Total **synthesis** of cryptoxanthin and a further synthesis of zeaxanthin
SO Helv. Chim. Acta (1957), 40, 456-67
AU Isler, O.; Lindlar, H.; Montavon, M.; Ruegg, R.; Saucy, G.; Zeller, P.
AN 1957:62225 HCAPLUS
DN 51:62225
OREF 51:11293i,11294a-f

L246 ANSWER 278 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Xanthinin, a monocarbocyclic sesquiterpenoid lactone
SO Chem. & Ind. (London) (1957) 328
AU Geissman, T. A.; Deuel, P. G.
AN 1957:62224 HCAPLUS
DN 51:62224
OREF 51:11293f-i

L246 ANSWER 279 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of polyisoprenoids. I. Synthesis of .beta.-hydroxy-.beta.-methylglutaric acid semialdehyde
SO Ann. (1957), 608, 71-8
AU Eggerer, Hermann; Lynen, Feodor; Rauenbusch, Erich; Kessel, Ingrid
AN 1958:77035 HCAPLUS
DN 52:77035
OREF 52:13633h-i,13634a-d

L246 ANSWER 280 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Metabolism of **acetate** in Hevea brasiliensis
SO Nature (London, United Kingdom) (1957), 180, 37
CODEN: NATUAS; ISSN: 0028-0836
AU Patrick, A. D.
AN 1958:73021 HCAPLUS
DN 52:73021
OREF 52:13012a-c

L246 ANSWER 281 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Mevalonic acid and **carotenogenesis** in Phycomyces blakesleeanus
SO Biochemical Journal (1957), 66, 31P-32P
CODEN: BIJOAK; ISSN: 0264-6021
AU Braithwaite, G. D.; Goodwin, T. W.
AN 1959:23880 HCAPLUS
DN 53:23880
OREF 53:4430a-c

L246 ANSWER 282 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Polyene diether acetals and their manufacture and conversion into polyene aldehydes
AN 1957:30032 HCAPLUS
DN 51:30032
OREF 51:5835b-f

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 753635		19560725	GB	

L246 ANSWER 283 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI 2,7-Dimethyl-2,6-octadien-4-yne-1,8-dial
AN 1956:89478 HCAPLUS
DN 50:89478
OREF 50:16862a-b

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 744890		19560215	GB	

L246 ANSWER 284 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The synthesis and configuration of neo-b vitamin A and neoretinene b
SO Journal of the American Chemical Society (1956), 78, 2651-2
CODEN: JACSAT; ISSN: 0002-7863
AU Oroshnik, Wm.
AN 1956:81938 HCAPLUS
DN 50:81938
OREF 50:15467h-i,15468a-c

L246 ANSWER 285 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The biosynthesis of .beta.-**carotene** by Mucor hiemalis. IV. The part played by acetic acid in the **synthesis** of the **carotene** molecule, especially positions 3,4,6 and 3',4',6', studied with the aid of carbon 14-labeled acetic acid
SO Helv. Chim. Acta (1956), 39, 1975-80
AU Grob, E. C.; Butler, R.
AN 1957:17881 HCAPLUS
DN 51:17881
OREF 51:3741h-i

L246 ANSWER 286 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenogenesis**. XVIII. **Carotenoid production** by a strongly chromogenic bacterium isolated from butter
SO Biochemical Journal (1956), 62, 275-81
CODEN: BIJOAK; ISSN: 0264-6021
AU Goodwin, T. W.; Jamikorn, Malini
AN 1956:40957 HCAPLUS
DN 50:40957
OREF 50:7935c-f

L246 ANSWER 287 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** in the **carotenoid** series. II. **Synthesis** of various ring components
SO Helvetica Chimica Acta (1956), 39, 259-73
CODEN: HCACAV; ISSN: 0018-019X
AU Isler, O.; Montavon, M.; Ruegg, R.; Zeller, P.
AN 1956:81940 HCAPLUS
DN 50:81940
OREF 50:15468h-i,15469a-i,15470a-b

L246 ANSWER 288 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Some new aspects of acetic acid involved in biosynthesis of .beta.-**carotene**
SO Chimia (Switz.) (1956), 10, 258-9
AU Grob, E. C.; Butler, R.

AN 1957:91830 HCAPLUS
DN 51:91830
OREF 51:16696b-d

L246 ANSWER 289 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** in the **carotenoid** series. XXXIV. **Syntheses** of C14- and C15-aldehydes
SO Ann. (1956), 598, 51-64
AU Inhoffen, Hans Herloff; Erdmann, Dietrich
AN 1956:81949 HCAPLUS
DN 50:81949
OREF 50:15474c-i,15475a-f

L246 ANSWER 290 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI An alternate fatty acid cycle involving thioesters of pantetheine
SO Journal of the American Chemical Society (1955), 77, 5194-5
CODEN: JACSAT; ISSN: 0002-7863
AU Stern, Joseph R.
AN 1956:5051 HCAPLUS
DN 50:5051
OREF 50:1107b-c

L246 ANSWER 291 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The biosynthesis of .beta.-**carotene** by Mucor hiemalis. The use of acetic acid in the **synthesis** of the **carotene** molecule, especially in positions 14-15, 14'-15' and 10-11, 10'-11', investigated with C14-acetic acid. III
SO Helvetica Chimica Acta (1955), 38, 1313-16
CODEN: HCACAV; ISSN: 0018-019X
AU Grob, E. C.; Butler, R.
AN 1955:78595 HCAPLUS
DN 49:78595
OREF 49:14904d-f

L246 ANSWER 292 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenogenesis**. XV. The role of carboxylic acids in the biosynthesis of .beta.-**carotene** by Phycomyces blakesleeanus
SO Biochemical Journal (1955), 60, 649-55
CODEN: BIJOAK; ISSN: 0264-6021
AU Friend, J.; Goodwin, T. W.; Griffiths, L. A.
AN 1955:78514 HCAPLUS
DN 49:78514
OREF 49:14886e-h

L246 ANSWER 293 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Evaluation of methyl esters, by-product of the extraction of **carotene** from palm oil
SO Oleagineux (1955), 10, 99-105,193-6,269-73
CODEN: OLEAAF; ISSN: 0030-2082
AU Jorand, J.
AN 1955:72026 HCAPLUS
DN 49:72026
OREF 49:13670e-g

L246 ANSWER 294 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenogenesis**. **Synthesis** of .beta.-methylcrotonic acid by Phycomyces blakesleeanus
SO Proceedings of the International Congress of Biochemistry (1955) 87
CODEN: 18USAR
AU Goodwin, T. W.; Modi, V. V.
AN 1956:74532 HCAPLUS
DN 50:74532
OREF 50:14052g-i

L246 ANSWER 295 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** of polyenes. VI. **Isoprenoid** polyenes containing sterically hindered cis configurations
SO Journal of the American Chemical Society (1954), 76, 5719-36
CODEN: JACSAT; ISSN: 0002-7863
AU Oroshnik, Wm.; Mebane, Alexander D.
AN 1955:77776 HCAPLUS
DN 49:77776
OREF 49:14702g-i,14703a-i,14704a-i,14705a-i,14706a-b

L246 ANSWER 296 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The biosynthesis of .beta.-**carotene** by Mucor hiemalis. The use of acetic acid in the **synthesis** of the **carotene** molecule, especially the ionone grouping, investigated with C14-acetic acid. II
SO Helvetica Chimica Acta (1954), 37, 1908-12
CODEN: HCACAV; ISSN: 0018-019X
AU Grob, E. C.; Butler, R.
AN 1955:12636 HCAPLUS
DN 49:12636
OREF 49:2567g-i

L246 ANSWER 297 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The exchange of **carotenoids** in higher plants
SO Zeitschrift fuer Botanik (1954), 42, 387-435
CODEN: ZBOTA3; ISSN: 0372-8102
AU Beekmann, Helga
AN 1955:33015 HCAPLUS
DN 49:33015
OREF 49:6396f-i

L246 ANSWER 298 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The effect of pantothenic acid, pantethine, and phosphorylated pantethine on **carotenoid** formation by Mucor hiemalis
SO Experientia (1954), 10, 378-9
CODEN: EXPEAM; ISSN: 0014-4754
AU Grob, E. C.; Grundbacher, V.; Schopfer, W. H.
AN 1955:5037 HCAPLUS
DN 49:5037
OREF 49:1113e-f

L246 ANSWER 299 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The biosynthesis of .beta.-**carotene** by Mucor hiemalis. The use of acetic acid in the **synthesis** of the **carotene** molecule investigated with C14-labeled acetic acid
SO Experientia (1954), 10, 250-1
CODEN: EXPEAM; ISSN: 0014-4754
AU Grob, E. C.; Butler, R.
AN 1954:60664 HCAPLUS
DN 48:60664
OREF 48:10796g-h

L246 ANSWER 300 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Studies of cholesterol biosynthesis. II. Distribution of **acetate** carbon in the ring structure
SO Biochemical Journal (1953), 54, 597-601
CODEN: BIJOAK; ISSN: 0264-6021
AU Cornforth, J. W.; Hunter, G. D.; Popjak, G.
AN 1953:66351 HCAPLUS
DN 47:66351
OREF 47:11279a-c

L246 ANSWER 301 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The biosynthesis of **carotenoids** by Phycomyces blakesleeanus

SO Internationale Zeitschrift fuer Vitaminforschung (1952), 23, 484-9
CODEN: IZVIAK; ISSN: 0020-9406
AU Grob, E. C.; Schopfer, W. H.; Poretti, G. G.
AN 1952:54871 HCAPLUS
DN 46:54871
OREF 46:9156h-i

L246 ANSWER 302 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Biosynthesis of **carotenoids**
SO Biochemische Zeitschrift (1952), 323, 376-81
CODEN: BIZEA2; ISSN: 0366-0753
AU Arnaki, M.; Stary, Z.
AN 1953:29064 HCAPLUS
DN 47:29064
OREF 47:4951b-d

L246 ANSWER 303 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Carotenogenesis** in Phycomyces blakesleeanus
SO Congres International de Biochimie, Resumes des Communications (1952) 210
CODEN: 20DPAQ
AU Goodwin, T. W.; Griffiths, L. A.; Jamikorn, Malini; Willmer, J. S.
AN 1956:1924 HCAPLUS
DN 50:1924
OREF 50:436c-d

L246 ANSWER 304 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** in the **carotenoid** series. XXIV. Attempts to prepare 3,3',4,4'-bisdehydro-.beta.-**carotene**
SO Ann. (1952), 578, 177-87
AU Inhoffen, Hans H.; Arend, Wolfgang
AN 1954:3541 HCAPLUS
DN 48:3541
OREF 48:652f-i,653a-g

L246 ANSWER 305 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The **synthesis** of .beta.-**carotene** by Phycomyces cultured in a medium containing sodium **acetate** as the only source of carbon
SO Experientia (1952), 8, 140
CODEN: EXPEAM; ISSN: 0014-4754
AU Shopfer, W. H.; Grob, E. C.
AN 1952:67547 HCAPLUS
DN 46:67547
OREF 46:11310c-d

L246 ANSWER 306 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Investigation of the biosynthesis of **carotenoids** by Sarcina lutea
SO Folia Pharmaceutica (Istanbul) (1952), 2, 115-18
CODEN: FOPMAS; ISSN: 0428-8300
AU Arnaki, M.; Stary, Z.
AN 1953:29088 HCAPLUS
DN 47:29088
OREF 47:4955a-c

L246 ANSWER 307 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The preparation of cyclic vinyl ethers
SO Journal of the American Chemical Society (1951), 73, 913-14
CODEN: JACSAT; ISSN: 0002-7863
AU Parham, Wm. E.; Holmquist, Howard E.
AN 1951:46987 HCAPLUS
DN 45:46987
OREF 45:7998c-g

L246 ANSWER 308 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The mechanism of rubber formation in the guayule. III. Experiments with isotopic carbon
SO Archives of Biochemistry and Biophysics (1951), 31, 234-47
CODEN: ABBIA4; ISSN: 0003-9861
AU Arreguin, Barbarin; Bonner, James; Wood, Betty Jean
AN 1951:31405 HCAPLUS
DN 45:31405
OREF 45:5439a-c

L246 ANSWER 309 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI The **production** of marked .beta.-**carotene** by Phycomyces blakesleeanus
SO Experientia (1951), 7, 218-19
CODEN: EXPEAM; ISSN: 0014-4754
AU Grob, E. C.; Poretti, G. G.; von Muralt, A.; Schopfer, W. H.
AN 1952:3039 HCAPLUS
DN 46:3039
OREF 46:568a-b

L246 ANSWER 310 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Ethyl sorbate in the diene synthesis
SO Journal of the American Chemical Society (1949), 71, 2865-8
CODEN: JACSAT; ISSN: 0002-7863
AU Rigg, M. Wesley; Rosenthal, Rudolph
AN 1951:5236 HCAPLUS
DN 45:5236
OREF 45:892c-h

L246 ANSWER 311 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** of **isoprenoid** compounds in plants
SO Journal of Chemical Education (1949), 26, 628-31
CODEN: JCEDA8; ISSN: 0021-9584
AU Bonner, James
AN 1950:17984 HCAPLUS
DN 44:17984
OREF 44:3576b-d

L246 ANSWER 312 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** in the **carotenoid** series. II. **Synthesis** of a hydrocarbon, C30H42
SO Ann. (1948), 561, 26-31
AU Inhoffen, Hans H.; Pommer, Horst; Bohlmann, Ferdinand
AN 1949:13106 HCAPLUS
DN 43:13106
OREF 43:2588d-i

L246 ANSWER 313 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Effect of various salts on the **synthesis** of ascorbic acid and **carotene** in cress seedlings
SO Biochem. J. (1947), 41, 197-205
AU Mapson, L. W.; Cruickshank, E. M.
AN 1948:2878 HCAPLUS
DN 42:2878
OREF 42:644h-i,645a

L246 ANSWER 314 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** of aliphatic terpene alcohols from **isoprene**
SO Ber. (1943), 76B, 831-46
AU Lennartz, Theo.
AN 1944:11772 HCAPLUS
DN 38:11772
OREF 38:1737g-i,1738a-i,1739a

L246 ANSWER 315 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** in the **carotenoid** series. V. Preparation of higher aliphatic polyenealdehydes
SO Ann. (1941), 547, 285-02
AU Schmitt, J.; Obermeit, A.
AN 1942:41253 HCAPLUS
DN 36:41253
OREF 36:6523g-h

L246 ANSWER 316 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** in the **carotenoid** series. IV. Preparation of .omega.-phenyl-and .omega.-furylpolyenealdehydes
SO Ann. (1941), 547, 270-84
AU Schmitt, J.
AN 1942:41252 HCAPLUS
DN 36:41252
OREF 36:6523e-g

L246 ANSWER 317 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Syntheses** in the **carotenoid** series. III. Preparation of a methyl homolog of dehydro-.beta.-cyclocitral
SO Ann. (1941), 547, 256-70
AU Schmitt, J.
AN 1942:41251 HCAPLUS
DN 36:41251
OREF 36:6522i,6523a-e

L246 ANSWER 318 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Synthesis** of terpenes from **isoprene**
SO Ann. (1932), 496, 52-77
AU Wagner-Jauregg, T.
AN 1932:41789 HCAPLUS
DN 26:41789
OREF 26:4320h-i,4321a-b

L246 ANSWER 319 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI Synthetic experiments with ethinylcarbinols. I. Transformation of 3-methyl-butinol into 3-methylbutenin, 3-methylbutanolone and its condensation products
SO Ber. (1922), 55B, 2903-23
AU Scheibler, Helmut; Fischer, Artur
AN 1923:8065 HCAPLUS
DN 17:8065
OREF 17:1419b-i,1420a-b

L246 ANSWER 320 OF 324 HCAPLUS COPYRIGHT 2003 ACS
TI **Making isoprene**
IN Webel, F.
AN 1914:19261 HCAPLUS
DN 8:19261
OREF 8:2816d-e

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 1098859		19140602	US	

L246 ANSWER 321 OF 324 NTIS COPYRIGHT 2003 NTIS
TI Biosynthesis of Membrane Lipids in Halobacterium Cutirubrum. Reprint: Biosynthesis of Membrane Lipids in Halobacterium Cutirubrum.
NR AD-679 417/XAB; NRC-10141
9p; 1968
AU Kates, M.; Wassef, M. K.; Kushner, D. J.
AN 1969(31):02662 NTIS

L246 ANSWER 322 OF 324 WPIDS (C) 2003 THOMSON DERWENT

TI **Prodn** of **isoprene**.
PI JP 46000161 B (197102)*

L246 ANSWER 323 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI Quat phosphonium salts as intermediates for **carotenoids**.
PI GB 1102064 A (196800)*
NL 6704300 A (196801)
US 3517067 A (197025)

L246 ANSWER 324 OF 324 WPIDS (C) 2003 THOMSON DERWENT
TI 3-methyl-but-2-en-1-ol or 3-methyl-but-2-en-1-yl.
PI BE 725088 A (196800)*
NL 6817562 A (196801)
CA 833592 A (197006)
FR 1594968 A (197042)
GB 1239434 A (197127)
DE 1643709 B (197128)
US 3655735 A (197218)
CH 525173 A (197237)
JP 48007408 B (197310)

=> save temp l246 lycopene/a
ANSWER SET L246 HAS BEEN SAVED AS 'LYCOPENE/A'

=> d ab 19,25,33-35,40,41,115,116,267

L121 ANSWER 19 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AB The invention is concerned with a multi-stage process for **making** an oxidative metabolite of the **carotenoid lycopene**, 2,6-cyclolycopene-1,5-diol having the formula ##STR1## In this process alpha-terpinyl **acetate** is oxidatively dihydroxylated to a cyclohexanediol (IV), the cyclohexanediol (IV) is oxidatively cleaved to a ketoaldehyde (V), the ketoaldehyde (V) is subjected to an intramolecular aldol condensation to give a cyclopentanol (VI), the cyclopentanol (VI) is silylated to its silylated derivative formylcylopentane (VII), the formylcyclopentane (VII) is subjected to a C3 -chain lengthening with acetone and simultaneously to a saponification for the cleavage of the acetyl group to give a cyclopentylbutenone (VIII), the cyclopentylbutenone (VIII) is reacted with vinyl magnesium bromide to give a pentadienol (IX), the pentadienol (IX) is converted with deprotection of the silylated hydroxy group into a phosphonium salt (X), this salt is subjected to a Wittig reaction with 2,7-dimethyl-2,4,6-octatriene-1,8-dial to give a tridecahexaenal (XII) and the tridecahexaenal (XII) is subjected to a Wittig reaction with a (3,7,11-trimethyl-dodeca-2,4,6,10-tetraenyl)triphenylphosphonium salt to give the desired 2,6-cyclolycopene-1,5-diol (II). A variant of this process, also in accordance with the invention, comprises converting the cyclopentylbutenone (VIII) into the phosphonium salt (X) via two alternative intermediates, namely a pentadienoic acid ester (XIV) and a different pentadienol (XV), into the same phosphonium salt (X). Moreover, the invention is concerned with the novel intermediates (V), (VI), (VII), (VIII), (IX), (X), (XII), (XIV) as well as (XV) and the individual process steps which lead to these novel intermediates. 2,6-cyclolycopene-1,5-diol is useful in the prevention of cancer growth in human cells.

L121 ANSWER 25 OF 324 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 12
AB In summary the biosynthetic pathway for the formation of **isoprenoid** compounds in plants is similar to the pathway of sterol biosynthesis in animals and yeast. In plants, **isoprenoids** are **synthesized** from acetyl-CoA via mevalonate and isopentyl pyrophosphate to long-chain prenyl pyrophosphates. These compounds may then be metabolized to form various **isoprenoid** compounds. The bovine corpus luteum, which utilizes the Porter-Lincon pathway, has been

shown to metabolize **acetate** to steroids and .beta.-**carotene**. For example, farnesyl pyrophosphate is an intermediate in the **production** of steroids and .beta.-**carotene**. The **synthesis** of **carotenoids** continues with the condensation of two molecules of geranylgeranyl pyrophosphate to phytoene (C40 hydrocarbon), phytofluene, and eventually to .beta.-**carotene**. .beta.-**Carotene** can then be metabolized to retinol. Retinol is important for the synthesis of cholesterol and the metabolism of various steroids, such as pregnenolone and progesterone. The action of vitamin A on progesterone metabolism is important for embryonic development.

L121 ANSWER 33 OF 324 HCAPLUS COPYRIGHT 2003 ACS

AB A review with 17 refs. on the novel 1-deoxy-D-xylulose-5-phosphate (DOXP) pathway of isopentenyl diphosphate (IPP) formation, which is located in plastids. Higher plants and several algae groups possess a dichotomy in their **isoprenoid** biosynthesis, whereby their plastidic **isoprenoids** are **synthesized** via the novel DOXP pathway. However, their cytosolic sterols are formed via the cytosolic **acetate**/mevalonate pathway of IPP formation. Various mono- and diterpenes are also formed via the plastidic DOXP pathway. Apparently, the DOXP pathway is present in all oxygen-evolving photosynthetic organisms. Data indicate that the prokaryotic chloroplasts as endosymbionts conserved their former bacterial DOXP pathway of IPP formation which appears to be as old as the **acetate**/mevalonate pathway that has been found in other bacterial groups.

L121 ANSWER 34 OF 324 MEDLINE DUPLICATE 16

AB For many years it was accepted that isopentenyl diphosphate, the common precursor of all **isoprenoids**, was **synthesized** through the well known **acetate**/mevalonate pathway. However, recent studies have shown that some bacteria, including Escherichia coli, use a mevalonate-independent pathway for the synthesis of isopentenyl diphosphate. The occurrence of this alternative pathway has also been reported in green algae and higher plants. The first reaction of this pathway consists of the condensation of (hydroxyethyl)thiamin derived from pyruvate with the C1 aldehyde group of D-glyceraldehyde 3-phosphate to yield D-1-deoxyxylulose 5-phosphate. In E. coli, D-1-deoxyxylulose 5-phosphate is also a precursor for the biosynthesis of thiamin and pyridoxol. Here we report the molecular cloning and characterization of a gene from E. coli, designated dxs, that encodes D-1-deoxyxylulose-5-phosphate synthase. The dxs gene was identified as part of an operon that also contains ispA, the gene that encodes farnesyl-diphosphate synthase. D-1-Deoxyxylulose-5-phosphate synthase belongs to a family of transketolase-like proteins that are highly conserved in evolution.

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AB Isopentenyl diphosphate, the common precursor of all **isoprenoids**, has been widely assumed to be synthesized by the **acetate**/mevalonate pathway in all organisms. However, based on in vivo feeding expts., isopentenyl diphosphate formation in several eubacteria, a green alga, and plant chloroplasts has been demonstrated very recently to originate via a mevalonate-independent route from pyruvate and glyceraldehyde 3-phosphate as precursors. Here we describe the cloning from peppermint (Mentha x piperita) and heterologous expression in Escherichia coli of 1-deoxy-D-xylulose-5-phosphate synthase, the enzyme that catalyzes the first reaction of this pyruvate/glyceraldehyde 3-phosphate pathway. This synthase gene contains an ORF of 2,172 base pairs. When the proposed plastid targeting sequence is excluded, the deduced amino acid sequence indicates the peppermint synthase to be about 650 residues in length, corresponding to a native size of roughly 71 kDa. The enzyme appears to represent a novel class of highly conserved transketolases and likely plays a key role in the biosynthesis of plastid-derived **isoprenoids** essential for growth, development, and defense in plants.

L121 ANSWER 40 OF 324 MEDLINE DUPLICATE 18
AB Labeling experiments using [1-13C]**acetate** or [1-13C]glucose were performed with opportunistic pathogenic bacteria, with innocuous bacteria related to pathogenic species or with phytopathogenic species. The labeling pattern was determined in the **isoprenic** moiety of ubiquinone or menaquinone derivatives. These experiments showed that Acinetobacter, Citrobacter, Erwinia, Pseudomonas, Burkholderia, Ralstonia and Mycobacterium **synthesize** their **isoprenoids** via the mevalonate-independent glyceraldehyde 3-phosphate/pyruvate route. Enzymes of this novel bacterial metabolic route, which is apparently absent in vertebrates and man, therefore represent potential targets for a novel type of antibacterial drugs.

L121 ANSWER 41 OF 324 HCAPLUS COPYRIGHT 2003 ACS
AB Factors affecting manuf. of **carotenoids** with photosynthetic Rhodopseudomonas sp. R-41. The yield of **carotenoid** was increased from 23.8 mg/g dry cell to 57.3 mg/g dry cell under the optimal conditions: **acetate** as C source, Na glutamate N source, yeast exts. growth factors, Mg2+ 4 mg/L, Fe3+ 2 mg/L, 1500 lx and incubation at 30.degree., micro-acerbic for 120 h.

L121 ANSWER 115 OF 324 HCAPLUS COPYRIGHT 2003 ACS
AB Wild-type P. blakesleeanus **synthesizes** the yellow pigment, .beta.-**carotene**. Color mutants exhibit various alterations in the biosynthesis of .beta.-**carotene** or in its regulation. The presence of certain chems. in the medium stimulates **carotenogenesis** in the wild type. Different mechanisms of action are attributed to agents which stimulate or fail to stimulate different sets of mutants; this is the case of retinol and di-Me phthalate. Di-Me phthalate and veratrol are active on the same mutants, and therefore are likely to act in the same way. The main regulation of **carotenogenesis**, end-product inhibition, does not operate in the mutants of certain genes; these mutants are indifferent to retinol. By using a collection of retinoids it was concluded that their action depends on their structural similarity to a part of the .beta.-**carotene** mol. These and other observations suggest that end-product inhibition of the pathway is mediated by a complex of .beta.-**carotene** and two gene products and that the retinoids compete with .beta.-**carotene** and prevent end-product inhibition.

L121 ANSWER 116 OF 324 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. DUPLICATE 50
AB Carefully isolated intact spinach chloroplasts virtually free of contamination of other organelles effectively form .beta.-**carotene** from NaH14CO3 or [U-14C]-3-phosphoglycerate (PGA) under photosynthetic conditions. The photosynthate pool formed in chloroplasts from 1 to 2 millimolar [U-14C]-3-PGA or 3 to 6 millimolar NaH14CO3 was fully sufficient to supply .beta.-**carotene synthesis** with intermediates for about 1 hour at maximal rates of about 20 nanomoles 14C incorporated per milligram chlorophyll per hour. Fatty acid synthesis remains, under these circumstances, in linear dependence to substrate concentrations with far lower activity. Isotopic dilution of the .beta.-**carotene synthesis** by adding unlabeled glyceraldehyde 3-phosphate, dihydroxyacetone-P, 3-PGA, 2-PGA, phosphoenolpyruvate, pyruvate, respectively, may be interpreted as a direct substrate flow from photosynthetically fixed CO2 to isopentenyl pyrophosphate synthesizing system. Unlabeled **acetate** did not dilute .beta.-**carotene synthesis**. Fatty acid **synthesis** acted similarly with unlabeled substrates; but it also was diluted by unlabeled **acetate**. These results indicate a tight linkage of photosynthetic carbon fixation and plastid **isoprenoid synthesis**.

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AB Microorganisms including numerous molds produce **carotenoids** from **acetate** and mevalonic acid. Phycomyces blakesleeanus and Mucor hiemalis, produce **carotenoid** as the principal substance. **Carotenogenesis** is induced by different carbohydrates, fatty acids, acids of the citric acid cycle, and pyruvic acid. With C14-**acetate** both C atoms of HOAc are incorporated into .beta.-**carotene**. The labeling pattern of .beta.-**carotene** conforms with that of squalene. With these microorganisms the **synthesis** of sterols and **carotenoids** runs parallel, suggesting a common **isoprenoid** precursor. Coenzyme A influences the formation of precursor as biosynthesis is increased by pantothenic acid, pantetheine and phosphorylated pantetheine which are essential constituents of coenzyme A. Mevalonic acid must be considered as the active or at least as related to the active **isoprenoid** precursor. C40 **carotenoids** are composed of 8 molecules of mevalonic acid. The C40 analog of squalene is lycopersene. The proposed pathway: tetrahydrolycopene, **lycopene** and .beta.-**carotene** is confirmed for this biosynthesis. The first **carotenoid** is **lycopene** and this is recognized as the precursor of all **carotenoids**. The pathway is **lycopene** , .gamma.-**carotene**, .beta.-**carotene**, .psi.-**carotene**-epoxide and mutachrome. Neurospora crassa grows in the dark with no **carotenoid production**, but upon exposure to light rapidly forms **carotenoids**. Cultures grown in the dark in a N atm. do not produce **carotenoid** until O is introduced. In the dark, more satd. **carotenoids** form in N. crassa indicating that .psi.-**carotene** and neurosporene are immediate precursors of **lycopene**. In 6 hrs. .delta.- and .gamma.-**carotene** appear. .gamma.-**Carotene** probably is derived from **lycopene** by ring closure. It is possible that **carotenoids** hydroxylated in the 3 or 3 and 3' positions derive from a colorless polyene.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
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